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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1946

ORIGINAL ARTICLES

THE THYROID AND BLOOD REGENERATION IN THE RAT

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(From Washington Square College of Arts and Science, New York University.)

It is generally known that the thyroid gland exerts some influence over the process of hemopoiesis. Reports on the nature of this relation, however, show many contradictions. For example, thyroidectomy is stated to: (1) cause an anemia;[2,3,8,11,15,16,19] (2) produce no change in red cell count;[13,35] (3) cause leukocytosis and relative lymphopenia;[3,13,15] (4) induce some leukopenia and lymphocytosis.[4,8,11] Further pertinent information is offered by Mannsfeld,[25] and Askanazy,[1] who found that thyroidectomized animals show a slow hemopoietic response to high altitudes, and by Furuya,[8] who noted a similar delay following hemorrhage. Meyer, Thewlis and Rusch[26] have reported, however, that thyroidectomized rats respond to the erythropoietic stimulation of reduced pressures in much the same way as do normal rats. In clinical hypothyroidism most investigators agree that there is an anemia[2,21,23,24] and a lymphocytosis,[14,21] but Wilson[35] reports a relative lymphopenia. In addition, Tatum[30] has found the marrow of cretins to be fatty and Watanabe[34] has reported that hypothyroidism results in a disorder of blood formation. Recently, Paul, Limarzi and Seed[27] have shown that thyroidectomy depresses erythropoiesis in polycythemic patients.

Studies of the blood picture in experimental and clinical hyperthyroidism also have yielded contradictory results. This condition has been reported to induce: (1) an increase in the number of red cells;[12,19,22,36] (2) an anemia, often preceded by a rise in erythrocyte number;[2,6,20,28,36] (3) leukopenia and lymphocytosis;[4,5] (4) leukocytosis involving granulocytosis;[22] (5) lymphopenia, granulocytosis and no change in total white cell count.[2]

These conflicting reports appear to indicate a need for additional and more highly controlled work on the subject. This investigation is concerned with the effects of hypothyroidism induced surgically or through thiouracil feeding, and of thyroxin on recovery from the anemia produced by hemorrhage in adult male rats. These results will be compared with those obtained with testosterone propionate and

cobalt nitrate. Use has been made before of the bled rat as a sensitive test animal for observing hemopoietic activities of hormonal or vitamin factors.[7,18] The present experiments include a study of red and white cells, hemoglobin, reticulocytes and bone marrow. A preliminary report on several phases of this work has already appeared.[9]

Materials and Methods. Thyroidectomies were performed under nembutal, and castrations under ether anesthesia. Initial counts of red blood cells (RBC), white blood cells (WBC), hemoglobin and reticulocytes were made on all animals. An anemia was induced by bleeding. From 4.25 to 6 cc. of blood, depending upon the weight of the animal, were withdrawn by cardiac puncture. Complete counts on each animal were made the day following bleeding and at weekly intervals thereafter. Subcutaneous injection of hormones and cobalt nitrate ($Co(NO_3)_2.6H_2O$) were begun the day after bleeding and continued daily throughout the course of the experiment.

Peripheral blood from the tail was employed and all counts were made in duplicate. Red cell counts were required to agree within $\pm 4\%$ and white cell counts within $\pm 10\%$. Reticulocyte counts were made from wet mounts of whole blood in 2% sodium citrate solution and stained with brilliant cresyl blue; 500 red cells were counted and the reticulocytes expressed as a percentage of these. Differential counts were made on smears of whole blood treated with Wright's stain. Hemoglobin content was determined with a Fisher electrohemometer.

For the bone marrow studies, the entire right femur was fixed in Downey's solution, decalcified in a mixture of equal parts of formic acid and 20% sodium citrate, dehydrated and cleared in dioxan, sectioned in paraffin and stained with hematoxylin and eosin or Kingsley's polychromatic solution. Smear preparations of marrow from the left femur were also made.

Results. SERIES 1. This consisted of 25 not operated upon and 24 thyroidectomized animals. These were subdivided the day after bleeding into the following groups: (1) 8 unoperated and 8 thyroidectomized rats receiving no treatment; (2) 8 unoperated and 8 thyroidectomized rats given 0.1 mg. thyroxin; (3) 9 unoperated and 8 thyroidectomized rats given 0.1 mg. thyroxin and 0.5 mg. testosterone propionate.*

1. *Effects of Thyroidectomy.* A survey of the initial counts before bleeding revealed no effect of thyroidectomy on the RBC and WBC 2 weeks after the operation. Hemorrhage caused no greater decrease in RBC than that shown by the unoperated controls. The return of the RBC, however, to normal levels was markedly inhibited in the thyroidectomized untreated group (Fig. 1). Hemoglobin regeneration was also slowed but not to as great a degree. With regard to total white count, the thyroidectomized group was the only one which showed a slow continued increase. However, the level at the end of the experiment was within the limits of the normal range. Reticulocytes appeared to be within normal limits throughout and the differential white cell counts revealed no significant change. The bone marrows of the thyroidectomized animals revealed some hypoplasia accompanied by a fatty infiltration, and a smaller erythroid/myeloid cell ratio than that observed in unoperated rats about 1 month after bleeding (Figs. 4 and 5).

Six rats were subjected to surgical procedure identical with that of thyroidectomy except that the thyroid was not removed. These animals showed a smaller decrease in RBC after bleeding than did the other groups. By the end of the 2nd week pre-bleeding levels were attained in all animals. In most respects this group did not differ significantly from the unoperated controls.

2. *Effects of Thyroxin.* In both the bled unoperated and thyroidectomized animals, thyroxin injections caused an increase in the rate of RBC regeneration (Fig. 1). This increase was relatively greater in the thyroidectomized than in the unoperated

* We wish to thank Dr. Erwin Schwenk, Schering Corporation, for the testosterone propionate.

groups. A marked stimulation of hemoglobin regeneration was noted in the thyroidectomized rats receiving this hormone. No consistent effects on the total or differential white cell count were observed. Reticulocyte numbers were increased above the hemorrhagic levels by thyroxin to a greater degree again in the thyroidectomized than in the unoperated groups. The vacuolar appearance of the marrow observed in thyroidectomized rats was considerably repaired by thyroxin (Fig. 6). The erythroid/myeloid cell ratios as determined from marrow smears were also significantly increased.

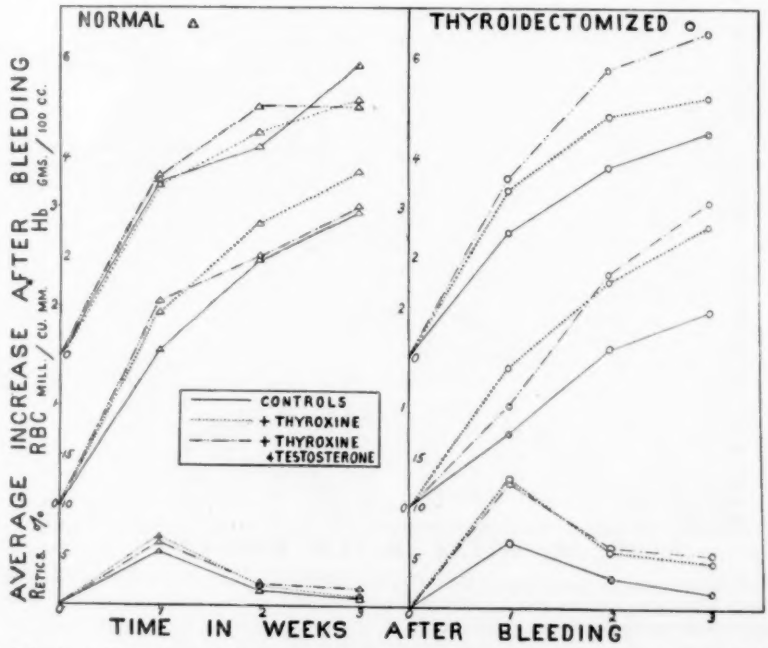

FIG. 1.—Effects of thyroxin and the combination of thyroxin and testosterone on average RBC, hemoglobin values and reticulocyte percentages in normal and thyroidectomized rats following bleeding.

3. *Effects of Thyroxin Plus Testosterone.* This combination of hormones produced the same general picture as thyroxin alone (Fig. 1). It caused, however, a more pronounced rise in hemoglobin in the thyroidectomized group.

SERIES 2. The 44 thyroidectomized animals were subdivided into the following groups: (1) 5 untreated; (2) 5 given 0.05 cc. sesame oil; (3) 6 given 0.1 mg. thyroxin; (4) 10 treated with 1.25 mg. testosterone propionate; (5) 6 given 0.1 mg. thyroxin along with 1.25 mg. testosterone propionate; (6) 6 treated with 1.25 mg. cobalt nitrate; and (7) 6 given 0.1 mg. thyroxin and 1.25 mg. cobalt nitrate. The results are shown in Figure 2.

1. *Effects of Thyroxin.* The picture found here was the same as in Series 1, *i. e.*, a more rapid return of RBC and hemoglobin to normal levels, marked reticulocyte response, no change in total and differential WBC count, and a stimulated marrow.

2. *Effects of Testosterone.* This hormone stimulated slightly RBC regeneration but produced a possible inhibition in hemoglobin production. Reticulocyte numbers were higher in this group during the 1st week of treatment. The bone marrow appeared normal.

3. *Effects of Thyroxin Plus Testosterone.* Except for a stronger hemoglobin and

reticulocyte response, the effects of this combination were quite similar to those produced by thyroxin alone.

4. *Effects of Cobalt.* This drug evoked as great a hemoglobin response as did thyroxin, and exerted a more powerful influence on RBC production. Reticulocytes were maintained at higher than normal levels. The bone marrows were markedly hyperplastic in all cases, revealing densely packed areas of erythrogenic cells.

SERIES 3. The animals were subdivided as follows: (1) 7 unoperated untreated; (2) 5 thyroidectomized untreated; (3) 8 thyroidectomized and castrated; (4) 7 thyroidectomized-castrated rats treated with 1.25 mg. testosterone propionate; (5) 8 unoperated fed a diet containing 0.2% thiouracil* 3 weeks prior to, and for 4 weeks following the bleeding. The results are depicted graphically in Figure 3.

It will be seen that castration in thyroidectomized rats did not cause a greater delay in RBC regeneration than that produced by thyroidectomy alone. Testosterone, which was only slightly effective in accelerating RBC regeneration in thyroidectomized rats (Series 2), proved to be a more potent stimulus in the thyroidectomized-castrated rat. Hemoglobin regeneration was more delayed in the thyroidectomized-castrated than in the thyroidectomized animal; this delay was over-

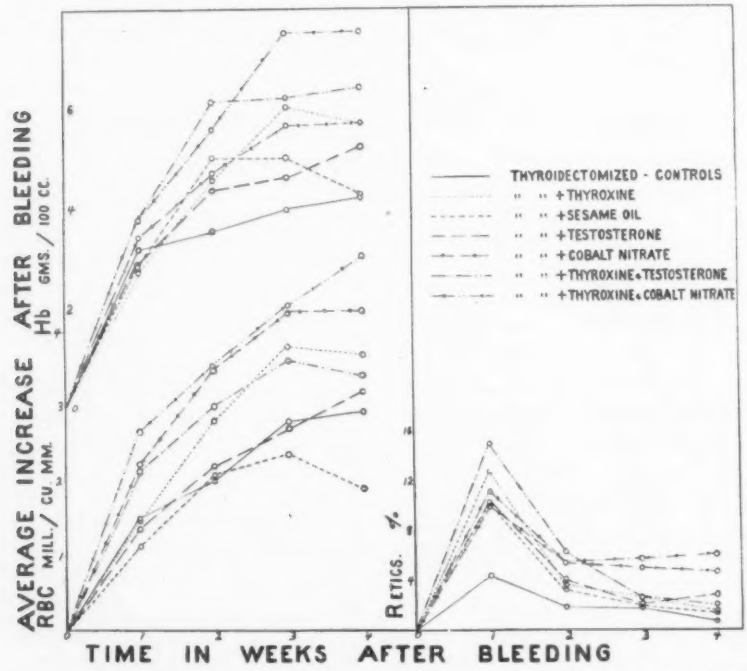

FIG. 2.—A comparison of the effects of thyroxin, testosterone, cobalt, thyroxin plus testosterone and thyroxin plus cobalt on average RBC, hemoglobin values and reticulocyte percentages in thyroidectomized rats following bleeding.

5. *Effects of Cobalt and Thyroxin.* This combination proved to be the most powerful stimulus in the series for RBC and hemoglobin regeneration and for high sustained reticulocyte values. The bone marrows were also intensely stimulated and the highest erythroid/myeloid cell ratios were encountered in this group (Fig. 7).

No significant trends could be detected in the total and differential WBC counts of any of the groups in this series.

* Dr. B. W. Carey, Lederle Laboratories, Inc., provided a generous supply of thiouracil.

come by testosterone injections. Thiouracil treatment inhibited both RBC and hemoglobin regeneration to about the same extent as that noted in thyroidectomized-castrated rats. Normal, thyroidectomized and thyroidectomized-castrated rats all displayed reticulocyte responses of approximately the same magnitude; testosterone treatment increased reticulocyte counts during the 1st week following bleeding but not beyond this period. Thiouracil fed rats possessed the smallest reticulocyte counts at all times during the experiment. White cell counts showed no significant alterations in any of the animals except for the thiouracil series in which the usual chronic granulocytopenic state was detected.[10]

Series 4. In the 3 series described above the thyroidectomized animals were employed 1 to 2 weeks following the operation. An additional experiment was performed to determine the type of result obtainable with long-time thyroidectomized rats. Accordingly 12 rats that had not been operated upon and 9 which had been thyroidectomized 6 months previously were divided into 2 groups the day after bleeding. Six unoperated and 5 thyroidectomized rats received daily injections of 0.1 mg. thyroxin and the other 10 served as untreated controls. The results corresponded in general to those obtained in the previous series of experiments. In this group, however, the delay in RBC and hemoglobin regeneration was strikingly apparent only during the 1st week following bleeding. Thyroxin exerted its usual stimulatory influence on the RBC, hemoglobin and reticulocyte values but to somewhat different extents in the unoperated and thyroidectomized groups. Again the total and differential white cell counts revealed no significant trends. A moderate tendency to hypoplasia noted in the marrows of the thyroidectomized animals in this series was corrected by the thyroxin treatment.

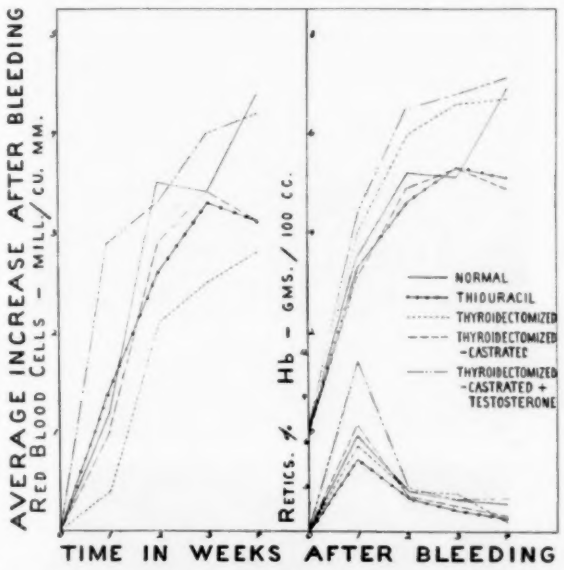

Fig. 3.—Effects of castration and testosterone plus castration on average RBC, hemoglobin values and reticulocyte percentages in thyroidectomized rats following bleeding. The influence of thiouracil on the behavior of bled unoperated rats is also seen.

Discussion. A definite relation between the thyroid gland and the process of erythropoiesis is indicated by the results of the present investigation. Support for this

contention comes from a study of both the peripheral blood picture and the bone marrow in bled animals. Thus thyroidectomy or hypothyroidism induced with thiouracil causes a marked delay in, and thyroxin injections an acceleration of RBC and hemoglobin regeneration in hemorrhagic anemia. The ability of thyroxin to stimulate RBC production has also been demonstrated in the hypophysectomized rat.[26,33]

The erythropoietic effect of thyroxin appears to be more evident in thyroidectomized than in unoperated animals. This may find its explanation in the different amounts of thyroid hormone existing in

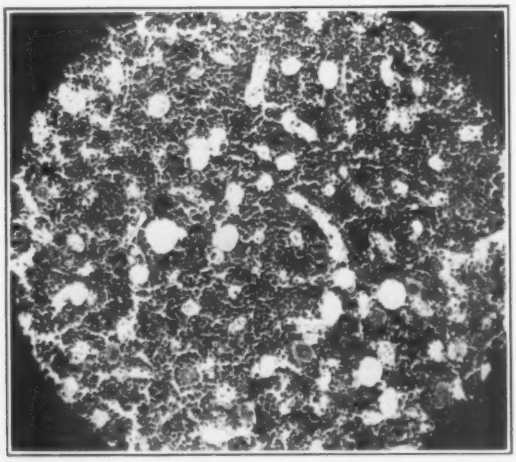

FIG. 4.—Bled rat unoperated upon and given no treatment. Some hyperplasia is still observed 30 days after bleeding. This and following figures represent median sagittal sections of rat femoral bone marrow, fixed in Downey's solution, decalcified in formic acid and sodium citrate, and stained with Kingsley's polychromatic solution. × 150.

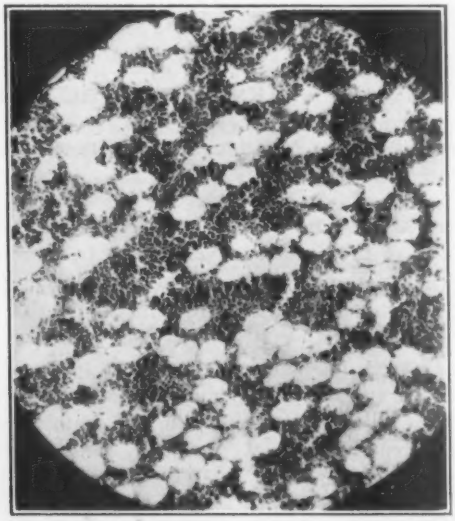

FIG. 5.—Bled thyroidectomized rat given no treatment. Fatty infiltration and slight hypoplasia of erythrogenic elements are apparent 30 days after bleeding (see Fig. 4).

the blood and in the reciprocal effects of this hormone on the anterior hypophyses of such animals. The "paradoxical" decrease in RBC count following an initial polycythemia induced by thyroxin[36] may perhaps be similarly explained.

Previous work[7] has shown that castration in the male delays the regeneration of red cells following bleeding. The present studies indicate, however, that castration superimposed upon thyroidectomy causes no further inhibition of RBC regeneration. Since testosterone has been shown to be a potent stimulus to erythrogenesis in the hypophysectomized rat[32] and in the castrated rat,[7,29] it was expected that this hormone would augment the action of thyroxin; this, however, did not occur. Moreover, testosterone, by itself, only slightly accelerated RBC regeneration in

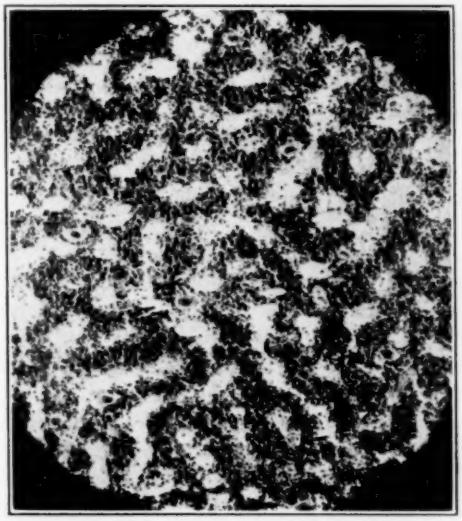

FIG. 6.—Bled thyroidectomized rat treated with thyroxin for 30 days. Considerable repair of the thyroidectomy hypoplasia is observed (see Fig. 5).

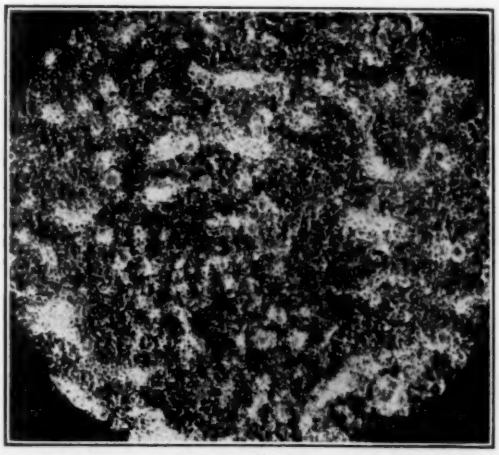

FIG. 7.—Bled thyroidectomized rat treated with thyroxin and cobalt for 30 days. Intense hyperplasia and hyperemia noted; many densely packed erythrogenic areas are visible.

bled thyroidectomized animals. This may have been due, in part, to a sensitivity of the thyroidectomized animal to sesame oil, the vehicle for testosterone. It is more likely, however, that injections of testosterone into thyroidectomized or unoperated animals, in which relatively high levels of endogenous male sex hormone already exist, are not effective as in hypophysectomized or castrated animals in which the male hormone concentration is low. Previous work[33] in addition has shown that daily injections of 2 mg. of testosterone are not as effective as 1 mg. doses. The fact that testosterone exerts a considerably greater effect in accelerating RBC regeneration in the thyroidectomized-castrated than in the thyroidectomized rat would lend additional support to this hypothesis.

The endocrine effects on hemoglobin synthesis are complex. Thyroidectomy inhibits and thyroxin stimulates hemoglobin regeneration in bled rats (the present work). On the other hand, testosterone depresses hemoglobin formation in the normal male rat and castration enhances it.[7] Difficult to reconcile with this is the fact that castration in the thyroidectomized rat further delays hemoglobin synthesis and testosterone accelerates its formation in the thyroidectomized-castrated rat; likewise the synergism of testosterone and thyroxin in speeding hemoglobin synthesis remains unexplained. It seems possible that, as for red cell numbers, hemoglobin values in endocrine-treated animals are determined by the relative levels of endogenous and exogenous hormones in the blood and the sensitivity of the bone marrow to hormonal stimulation under these conditions.

The results obtained from the peripheral white cell studies were disappointing. No significant trends were observed in any of the animals with the exception of 1 thyroidectomized group which displayed a rise in total white cell count, but even this was transient and soon disappeared. The absence of positive effects on the white cell picture does not necessarily constitute satisfactory evidence that the regeneration or distribution of these elements is not influenced by thyroid absence or excess. A considerable variation in leukocyte count has been usual among normal noninfected rats of our colony and this would tend to militate against the use of such animals for studies involving relatively small changes in white cell numbers.

Korenchevsky and Hall[17] have asserted that it is not possible to know whether the effects of sex hormones on the blood are due to changes in bone marrow activity or blood volume. They claim that variation in fat content of the marrow, one of the criteria employed by us in this as well as previous studies, "cannot be used as a reliable diagnostic feature of hemopoietic activity." We cannot agree entirely with this statement, for if fat does invade the marrow and replaces blood-forming tissues, the total hemopoietic activity is most likely depressed. Although it may be true, as they have found, that in certain experimental conditions (*e. g.*, after castration) the quantity of marrow fat is proportional to that found distributed throughout the body, this does not hold in every case. For example, it has been shown[31] that after hypophysectomy the marrow becomes hypoplastic and infiltrated with fat; this extensive vacuolization obviously cannot be explained in terms of an increased fat content of the body following hypophysectomy. In addition it should be emphasized that the fat content of the marrow has not been employed as the sole criterion in interpreting peripheral blood changes. The conclusions that the hormones affect the erythropoietic process itself in previous work[32,33] and in this report have been based on a combination of several points of evidence, *e. g.*, reticulocyte behavior, marrow histology and cytology, and the general lack of correlation between changes in red cell numbers and hemoglobin concentrations in the peripheral blood.

It is still an open question as to whether the thyroid directly regulates the erythropoietic process or whether this control is

a secondary manifestation of the changes in general metabolism induced by the gland. Excess or diminishing thyroid activity is also associated with changes in pituitary function and these too may exert an influence on erythropoiesis. A true answer to the problem of direct or indirect control of hemopoiesis could possibly be gained by studying the activity of bone marrow in tissue culture under the influence of hormonal agents.

In these studies the combination of thyroxin and cobalt produced the greatest stimulatory influence on red cell and hemoglobin regeneration, reticulocyte numbers and bone marrow activity. Cobalt has also been shown to act synergistically with testosterone in accelerating erythropoiesis.[7] It is suggested that small amounts of this metal be administered along with the appropriate hormones in the treatment of clinical anemias accompanying endocrine deficiency.

Summary. (1) Thyroidectomy or thiouracil treatment inhibited the return of RBC and hemoglobin to normal levels following bleeding. Studies of leukocyte changes were inconclusive. Injections of thyroxin speeded regeneration of RBC and hemoglobin to a greater degree in bled thyroidectomized than in bled unoperated rats.

2. Castration in thyroidectomized animals did not further delay RBC regeneration, but caused a greater inhibition of hemoglobin synthesis. Testosterone was a more effective erythropoietic agent in the thyroidectomized-castrated than in the thyroidectomized rat. The combination of testosterone and thyroxin was little more effective than thyroxin alone.

3. Cobalt markedly stimulated RBC and hemoglobin production in bled thyroidectomized rats; the combination of cobalt and thyroxin was even more powerful.

4. The hormones and cobalt, alone or in combination, all evoked marked reticulocytosis during the week following bleeding; but cobalt, and cobalt in combination with thyroxin, were the only treatments which maintained the reticulocytes at high levels throughout the experiment.

5. Neither thyroidectomy nor administration of the hormones or cobalt caused any significant change in the total or differential white cell counts of bled rats.

6. The bone marrow of thyroidectomized rats displayed a slightly greater state of hypoplasia and a lower erythroid/myeloid cell ratio than seen in animals not operated upon 3 to 4 weeks after the bleeding. Thyroxin tended to correct these changes; but cobalt, and especially the combination of cobalt and thyroxin, produced the greatest degree of marrow hyperplasia.

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THE USE OF RADON OINTMENT IN THE TREATMENT OF LATE IRRADIATION ULCERS

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A half century ago, Roentgen announced to the world, his epoch-making discovery of the rays that bear his name. It did not take long for the medical profession to learn that their diagnostic and therapeutic possibilities were fraught with a danger which soon tempered its early enthusiastic response, 200 late radiation injuries having been compiled in the first 7 years.[1] While the science of radiology has progressed to the point where it now rests on a firm foundation, only recently have measures been devised which counteract successfully some of the harmful effects of radiation.

There is no essential difference between the reaction caused by Roentgen rays and those effected by radium. The dosage usually is so planned that the maximum safe reaction becomes manifest. If the skin tolerance is exceeded, ulceration and necrosis may occur. The ulcer may heal, but the tissues are atrophic and are susceptible to slight trauma. In such areas, late radiation ulcers sometimes develop. The late changes due to radiation are hyperpigmentation, or loss of pigmentation, sparseness or absence of hair, few or numerous telangiectases, diminished or absent activity of sweat and sebaceous glands and various degrees of skin atrophy, keratoses, late ulceration or cancer.

Histologically, the immediate initial change[10] following irradiation is a focus of local edema and infiltration of leukocytes in the corium, followed by degeneration of the nuclei. The intimal cells of the blood-vessels of the corium and subcutaneous tissues undergo swelling, subsequently causing obliteration of the lumina. The larger vessels show similar changes, with thickening of the adventitia and media, and partial or complete occlusion. There are areas of varying sizes of necrosis in the corium, with loss of the epidermal appendages. The collagen shows various degrees of homogenization up to extensive fibrosis with the formation of dense sclerotic areas of connective tissue.[11] Later, there may be new formation of capillaries arising from the thickened vessels of the upper cutis. Sebaceous glands are destroyed and hair follicles are next in their degree of susceptibility.

Late radiation ulcers occur months to years after radiation has been employed. The ulcers usually follow infection or trauma of a minimal nature to an area showing the stigmata of previous radiation. In some cases, the trauma may be so minimal that the patient does not remember the incident. As a result of a diminished blood supply in the tissue, an ulcer forms which is indolent, usually quite painful and tender. The ulcers may become gangrenous and undergo malignant degeneration.[1] The pain may be so intense that the patient may develop drug addiction and become a total invalid. In addition, the medical profession cannot afford to minimize the medico-legal aspects of the problem.

It long has been known that individuals vary in their susceptibility to radiation[9] and that different regions of the body manifest different responses to an erythema dose.[5] The aged are usually less sensitive than infants, whereas females are usually slightly more sensitive than males. A coarse skin or anemic skin will react

less rapidly than thin skin or skin possessing good color. Blondes are usually more susceptible than brunettes, and Negroes are most resistant. The scalp is the least sensitive area, while the face is probably the most sensitive. The extensor surfaces are more resistant than the flexor surfaces, while the flexures such as the axilla and groin are very sensitive. Chemical irritants enhance the irradiation effect. Finally, a small treatment area wil ltolerate considerably more irradiation than will a large area.

The initial response of the skin to radiation is not always comparable with the delayed effects. An area of skin which shows a minimal initial susceptibility, as evidenced by the time of appearance and degree of erythema, may undergo late radiation necrosis following a dose that more susceptible areas would tolerate with safety. Thus, relatively ischemic areas may break down, despite exhibition of only minor primary radiation effects. This probably accounts for a certain irreducible percentage of late radiation ulcers.

With the advent of heavily filtered, exceedingly high voltage radiation (1000 kv.) it has been possible to deliver a tumor dose deep in the tissues with less effect on the skin than is obtained with the customary deep voltage (200 kv.) therapy.[12] Despite the refinements in equipment and in technique, however, radiology departments throughout the country continue to see late radiation ulcers, indicating the importance of dosage factors and individual susceptibility.

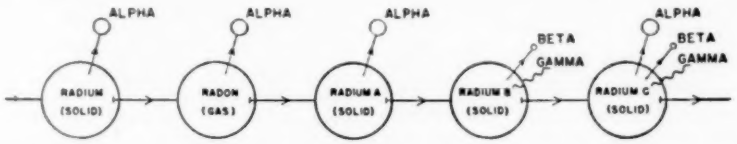
The toll exerted on the early workers in the profession[1] was the result of ignorance of the harmful possibilities of the new rays. It is therefore somewhat startling that, of 70 cases of radiation injuries recently seen by Uhlmann,[13] 35 were in physicians. Rather significant is the fact that the radiologists, that section of the medical profession most exposed to irradiation, but at the same time keenly aware of its potential dangers, were represented by only 3 members. Only 30 of the 70 cases received their injuries as a result of treatment with Roentgen rays and radium, the remainder being injured in the course of diagnostic or technical work. Of the 30 cases, but 14 had received therapy for malignancy. Of 37 cases of late radiation ulcers reviewed by Davis,[3] 27 were the result of treatment for benign conditions, 6 were the result of accidental irradiation during fluoroscopic procedures, and 4 resulted from irradiation for malignancy. What better evidence is needed that most radiation injuries are avoidable?

Until recently, these ulcers were notoriously refractory to medical treatment. The previous methods employed were varied, and the good results obtained were the exception rather than the rule. Periarterial sympathectomy, variations of acid-base equilibrium, salt-free diet, cod-liver oil ointment, ultraviolet irradiation and autohemotherapy all experienced temporary popularity, soon to be relegated to the medical limbo. The use of the fresh whole leaf of *Alœ vera* gave more encouraging results than any previous non-surgical method of therapy,[7,16] but it failed to produce the anticipated high percentage of cures. Plastic repair was necessary in many cases as the only means of cure.

In 1930, Uhlmann first began to use radon ointment in the treatment of late irradiation ulcers and has since that time effectively demonstrated its value as a therapeutic agent.[13,14,15] The active principle in the radon ointment is its high concentration of alpha particles and to a less extent beta particles and gamma radiation released by the atomic disintegration of the radon gas. Of 70 cases treated in this manner, only 2 were not cured, and these had residual carcinoma in them.

Radon Ointment Preparation. Radon ointment is prepared by dissolving radon under pressure in lanolin. Radon occurs normally in the gaseous state and is given off by radium prepared in the form of an aqueous solution of one of its salts. As the gaseous radon is formed, it bubbles up through the solution of radium and can be collected, purified, concentrated and measured in a closed system.

Radium becomes radon by the spontaneous emission from its nucleus of an alpha particle. Alpha particles are fast traveling nuclei of helium atoms which can be stopped by a sheet of paper, can penetrate tissue to a depth of only 0.030 to 0.050 mm., and are completely stopped by the material in the walls of the ordinary radium containers. Thus, they are not utilized when radium is used therapeutically in closed containers. Eventually, they annex 2 electrons and become helium atoms.



AW	226	222	218	214	214
AN	88	86	84	82	83
HL	1590	3.82	3.0	26.8	19.7
	Years	Days	Minutes	Minutes	Minutes

Disintegration of radium and its immediate descendants. *AW*, atomic weight; *AN*, atomic number; *HL*, half-life.

FIG. 1—Radom And Its Short Lived Disintegration Products. (Glasser, Quimby, Taylor, Weatherwax: Physical Foundations of Radiology, New York and London, Paul B. Hoeber, Inc., 1944.)

TABLE 1.—THE RADIOACTIVE DECAY OF RADON

Elapsed time	Fraction remaining	Elapsed time	Fraction remaining
0	1.000	3 days	0.581
4 hours	0.970	4 "	0.484
8 "	0.941	5 "	0.404
12 "	0.913	6 "	0.337
16 "	0.886	7 "	0.281
20 "	0.860	8 "	0.235
1 day	0.834	9 "	0.196
2 days	0.696	10 "	0.163

The residual activity after any other time interval can be computed from this table by multiplying the appropriate factors: for example, after 3 days 20 hours the fraction remaining is the product of the values for 3 days and for 20 hours, thus $0.581 \times 0.860 = 0.500$; after 15 days the fraction remaining is the product of the values for 10 days and for 5 days, $0.163 \times 0.404 = 0.066$. (Evans, R. D., Massachusetts Institute of Technology, Cambridge, Mass., in process of publication. Physical Constants of Radon Ointment.)

In less than 4 days, one-half of a given amount of radon will have disintegrated into a new element of lower atomic weight, losing an alpha particle and becoming Radium A. Even more rapidly, Radium A loses an alpha particle and becomes Radium B. This disintegrates in a matter of minutes to Radium C through the spontaneous emission of beta and gamma radiation.

The beta particles produced by the disintegration of Radiums B and C are high speed electrons which can penetrate tissue to a depth of 15.4 mm., but are stopped, as are the alpha particles, by the walls of the ordinary radium containers now in use. The gamma rays, which are the rays commonly employed in radium therapy, are electromagnetic in nature, with properties similar to light. They correspond to Roentgen rays, but are much shorter in wave length and are much more penetrating, only 50% being absorbed by 13 cm. of tissue.

Commercial radon contains radon, Radiums A, B and C, and continues to emit alpha, beta and gamma radiation, in unvarying fixed proportions for 30 days. Each day it loses 18% of its strength of the previous day. During the entire period of its activity, 90% of its emissions are alpha particles.

The question will naturally arise in the reader's mind as to why the gamma rays being emitted from the radon ointment will not produce still further damage to

the tissue already injured by overexposure to this type of radiation. Three factors are involved in explaining this apparent therapeutic paradox:

1. The amount of radon incorporated into the ointment is very small. The absolute concentration of gamma radiation emitted from the ointment during an 8 hour application in commonly employed therapeutic strength (200 e.s.u.) is 3.3×10^{-5} mc. hours, as contrasted to 5000 mc. hours commonly employed in the treatment of carcinoma of the cervix.

2. Due to its great penetrability, only a small amount of the gamma radiation is absorbed in the most superficial layers of the treated tissue.

3. Ninety % of the radiation is composed of alpha particles. In the superficial layers of tissue where all the energy from the alpha rays is absorbed, the amount of energy absorbed from the alpha rays is more than 10,000 times that absorbed from the gamma rays.[4]

Thus, the treated area receives an insignificant amount of gamma radiation and a high concentration of alpha radiation.

At the present time, nothing is known concerning the mode of action of radon in promoting the healing of ulcers. It is believed that capillary proliferation is stimulated in the ordinary avascular bed of the ulcer. Griffith[5] has shown that radon ointment applied to the skin causes an increase in the cutaneous capillary count.

Method of Treatment. When late radiation ulcers are seen for the first time by the radiologists, it is important to determine whether there is any evidence of malignancy. We believe that a biopsy should be performed in any suspicious case. In large ulcers, it may be necessary to perform multiple biopsies of all the areas under suspicion. Contrary to the experience of Uhlmann and Grossman,[15] who believe that a prompt response to radon ointment will tend to exclude the recurrent or residual malignancy, it has been our observation in 2 cases (Cases 7 and 12) that such a diagnostic criterion is not always reliable. It should be remembered that biopsy, performed on heavily irradiated tissue, is often inconclusive, for bizarre, edematous cells in an ulcer, the result of prolonged ischemia, may be mistaken for tumor cells.

Varying degrees of infection are present in most of the ulcers. In the majority, the infection is minimal and requires no adjuvant treatment. In some cases, the presence of an adherent slough or necrotic tissue will act as a mechanical barrier to the penetration of the alpha particles and will require preliminary treatment with zinc peroxide, or sulfanilamide-allantoin ointment for several days. Where these changes are not marked, one may be able to institute the course of radon therapy and apply the measures for combating infection in the intervening periods.

The ointment should be applied as close as possible to the viable tissue. This requires that the ulcer be thoroughly cleansed, débrided and dried. In this manner, the lanolin base has an opportunity to be absorbed into the deeper layers of the tissue and thus increase the depth of effective treatment past the 0.1 mm. range of the alpha particle. Care should be taken not to allow the ointment to come in contact with the operator's hands, the material being applied by means of a wooden tongue blade. It is applied evenly over the lesion, including a periphery of normal tissue, in a thickness of about 1 mm., 1 cc. covering approximately 10 sq. cm. of a lesion. The dressing applied over the ointment must be air-tight and this is achieved by the use of a rubber dam, oil silk, or cellophane which is fastened down with overlapping adhesive strips or scotch tape. In some cases, it may be desirable to apply gauze on top of the air-tight dressing before securing it with adhesive. When there is a pronounced secretion, it may be advisable to reverse the procedure and apply a thin layer of gauze on top of the ointment, followed by the protective dressing and adhesive. Liquid adhesive has been used at the periphery of the protective covering to further seal in the radon gas. The location of the lesions in various irregular contours of the body will often tax the ingenuity of the physician in devising methods of guaranteeing an air-tight dressing. After a specified time, the patient removes the dressing and following superficial cleansing, applies either a bland ointment such as boric acid ointment, or a bactericidal preparation

if deemed advisable. Irritating medications and prolonged exposure to strong sunlight are prohibited.

The dosage employed is a matter of experience. The ointment is obtainable commercially in 4 strengths: 100, 200, 500 and 1000 electrostatic units per cc. These concentrations equal the commercial Alphatron's 40, 80, 200 and 400 μc. per cc. The radon concentrations also are graded as *mild*, *moderate*, *strong* and *special*, corresponding to the strengths mentioned above. It has been our practice to apply the 200 e.s.u. ointment for 8 hours, once a week. If the response is slow, one may increase the period of application for any period up to 24 hours once a week. In some instances, we have employed two 8 hour applications per week. In some of our early cases, we used 100 e.s.u. but gave this up in favor of the 200 e.s.u. strength. We have never used the 1000 e.s.u. concentration.

Case Abstracts. Case 1. A white male, aged 70, treated for epithelioma on the dorsum of the right hand; 6670 r were delivered in 6 equal doses on Chaoul apparatus, June 6 to July 11, 1942. The factors were: 45 kv.p. with 0.2 mm. of nickel filtration at 5 cm. T.S.D. through a 3 cm. portal. It was completely healed in January 1943. He scratched his hand in January 1945 with formation of radiation ulcer 3 cm. in diameter. Twenty-five radon ointment treatments were given between Feb. 1, 1945, and May 22, 1945, which healed the ulcer; 200 e.s.u. strength for 24 hours used twice a week.

Case 2.—A white male, aged 41, treated for epithelioma on the dorsum of the right hand; 1200 mg. hours of radium in contact, filtered with 2 mm. of brass given in July 1930, plus 1550 r in 1 dose at 130 kv.p., 25 cm. T.S.D., with no added filter and 2 cm. portal. It was completely healed in September 1930. It broke down in January 1943; 100 e.s.u. radon ointment applied for 8 hours once a week for 10 weeks. It was completely healed by June 1943. In October 1943, he developed a keratotic horn at the site of ulcer. This finally broke down in October 1944. This second radiation ulcer did not respond to radon ointment and the area was skin grafted with a good result.

Case 3.—A white male, aged 68, treated for epithelioma on the dorsum of the left hand. The lesion received 8000 r at 25 cm. at 130 kv.p. with 1 mm. of Al filtration through a 3 cm. portal, between Feb. 14 and Feb. 21, 1939, in 6 equal doses. It was completely healed in May 1939. After trauma to hand in October 1942, an ulcer appeared. Radon ointment applied 60 times during the entire year of 1943 showed no result. After a pathologic fracture of the underlying metacarpal in June 1945, the ulcer healed spontaneously.

Case 4. A white male, aged 42, treated for eczema. This patient had 1 minute treatments 2 to 3 times a week over a 2 year period from a dermatologist in 1928 and 1929. The exact dosage and factors are unknown. Fissures developed in the skin of the right hand in 1940. Twenty-seven applications of radon ointment 100 e.s.u. strength twice a week for 8 hours showed only a slight improvement.

Case 5. A white female, aged 49, treated for hyperthyroidism at another hospital. Statement made by physician that 300 r were given to each of 4 portals in 1939; 1 of the 4 10 x 10 cm. portals had a severe reaction. The factors used were: 135 kv.p. at 30 cm. with 4 mm. Al filtration. In 1943, this area showed late irradiation changes and a 2 cm. portion of it ulcerated; 100 e.s.u. radon ointment applied for 8 hours once a week, completely healed it. Another area in this treatment portal broke down 6 weeks later. Similar treatment over a period of 11 weeks healed it.

Case 6. A white female, aged 43, treated for hyperthyroidism. She received 12,000 r over the anterior neck through a 10 x 13 cm. portal between June 1933 and September 1944 in 400 r doses. The factors were: 135 kv.p. at 30 cm. with 0.25 mm. of copper filtration. Severe later radiation dermatitis developed over the anterior portion of the neck in 1942. This ulcerated in 1945. Application of 200 e.s.u. radon ointment once a week for 8 hours produced marked improvement and 2 months later the ulcer healed, despite the fact that no further radon ointment had been given. Healing was complicated by an urticaria produced by sensitivity of the skin to adhesive tape.

Case 7. A white male, aged 69, first seen in 1940 with a basal cell carcinoma on the neck which had been present for 12 years and had reached a diameter of 4 cm.; 7500 r were delivered to the lesion by Chaoul therapy through multiple portals to provide uniform distribution of the above dose. The

factors were: 45 kv.p. with 0.2 mm. of nickel at a distance of 3 cm. The lesion healed slowly, the result being thin atrophic skin over a thick fibrous layer bound down to the deep fascia of the neck. It was always nodular. In 1941, a small ulcer developed in it and off and on during the next 2 years there were recurrent ulcerations in this scar that would heal slowly under sulfonamide ointments. In February 1943, 3 ulcers were present in the scar, 1 in the mid-line and 1 to each side of it. Biopsy showed residual basal cell carcinoma in 2 of them. In the next 3 months he received weekly 8 hour applications of 100 e.s.u. radon ointment. In July 1943, all the ulcers were healed. A small ulcer appeared at the site of the previous middle ulcer 3 months later and in the next year gradually enlarged to a diameter of 1.2 cm., despite the use of radon ointment. In September 1945, it measured 2 x 3 cm.

Case 8. A white male, aged 55, first seen in November 1941 for a 1.3 cm. basal cell carcinoma involving the inner canthus of the right eye. It was treated with 9000 r on the Chaoul apparatus in 22 equal doses. The factors were: 45 kv.p. with 0.2 mm. of nickel at a distance of 3 cm., through a portal 2 cm. in diameter. Fifteen months later, an irradiation ulcer 1.5 cm. in diameter appeared. He had increasing pain for 2 months. At that time, 100 e.s.u. radon ointment was applied for 8 hours weekly for 3 weeks. The lesion was practically healed 1 week after the second application. It has remained healed.

Case 9. A white male, aged 62, first seen in March 1941, with a 0.75 x 1.5 cm. basal cell carcinoma on the right cheek near the outer canthus. This was treated with 487 mg. hours of radium within 3 days at 1 cm. distance using 1 mm. platinum filtration. This was followed in June 1941 with 9000 r in 28 equal daily doses using 200 kv.p. with 2 Thoreous filtration through a 5 cm. portal at 25 cm. distance. The lesion was entirely healed in July 1941, but it broke down in January 1943. At this time 100 e.s.u. radon ointment was applied for 8 hours weekly for 3 weeks. The lesion was completely epithelialized 1 week after the second treatment. It has remained healed.

Case 10. A white male, aged 59. In July 1940, he received 6300 r in 4 equal weekly doses on the Chaoul apparatus for an epithelioma at the base of the right ala nasæ. In August 1940, he received 3900 r in 3 weekly equal doses using 200 kv.p. with 0.5 mm. of copper filtration through a portal 5 cm. in diameter at a distance of 25 cm. The lesion was entirely healed by November 1940. The site ulcerated in January 1942, and he suffered intolerable pain in this area until consulting the authors in December 1942 for a 1 cm. ulceration; 100 e.s.u. radon ointment used for 8 hours once weekly for 5 weeks healed the ulcer. There was little discomfort after the second treatment.

Case 11. A white male, aged 61. In 1939 this patient was seen with an 8 x 4.5 cm. basal cell epithelioma on the left side of the nose involving the cartilage of the nose; 2500 r in 13 equal daily doses were delivered at 25 cm. at 200 kv.p. with 0.5 cm. filtration. The lesion healed but the patient returned with an extensive recurrence with further invasion of the nasal cartilage in April 1944. He then was given 4300 r on the Chaoul apparatus with a daily dosage of 500 r. At the same time, 1900 mg. hours of interstitial radium therapy was given, using 0.5 mm. platinum needles. The lesion then healed slowly and by January 1945 there was only a 0.5 cm. ulcer left. During the winter cold weather, it broke down rapidly. Repeated biopsy showed no evidence of malignancy. In February 1945, 200 e.s.u. radon ointment was started and 24 weekly applications for 24 hours healed the ulcer entirely.

Case 12. A white female, aged 56. This patient had carcinoma of the left breast which had developed in 1942. In June 1943, there was extensive skin involvement with a 3 x 4 cm. node in the right upper quadrant that was beginning to ulcerate. Three 20 x 20 portals over the left breast received 1400 r each at 200 kv.p., 0.5 mm. Cu filtration at 50 cm. In April 1944, there was a foul infected ulcer in the left pectoral fold 3 cm. in diameter and 4 cm. deep. There was also a cancer encuirasse with nodes in the axilla. After secondary infection was cleaned up with zinc peroxide, 200 e.s.u. radon ointment was applied for 24 hours twice a week for 12 weeks. A senior medical student became interested and spent an hour daily dressing patient. Ulcer almost completely healed.

CASE 13. A white male, aged 60. In September 1942, he received 3200 r to a 3 x 6 cm. portal on the anterior thigh. There were 6 equal doses delivered 48 hours apart. In December 1943, an ulcer developed. This was treated with 100 e.s.u. radon ointment for 8 hours once a week for 19 weeks and resulted in complete healing. The factors were: 200 kv.p. at 15 cm. with 2 Thoreous filtration.

CASE 14. A white male, aged 50. Experimental irradiation. In August 1942, this patient received 3465 r in a period of 15 days. There were 6 treatments varying in intensity from 230 r to 924 r; 200 kv.p. was used at a distance of 15 cm. with a 2 Thoreous filter to a 3 x 6 cm. field. An ulcer developed in March 1944; 200 e.s.u. radon ointment applied twice weekly for 12 to 24 hours over a period of 25 weeks healed the ulcer completely.

CASE 15. A white male, aged 49. For a neurogenic sarcoma over the internal malleolus of the right leg, the patient received in 1932, 6000 r in 8 equal treatments over a period of 8 months, 135 kv.p. 30 cm. T.S.D. 1 mm. of Al. Recurrence in 1935 was removed surgically. Radiation ulcer developed in 1938. This healed slowly and spontaneously in the next 2 years. He developed a fungus infection over this site in 1943 in New Guinea and a radiation ulcer soon developed. Treatment was started in April 1945 with 200 e.s.u. radon ointment. It was applied for 48 hours twice a week for 1 month. The ulcer was completely healed at the end of that time.

CASE 16. A white male, aged 58. In 1937 and 1938, the patient treated himself twice a week on a low voltage therapy tube for dermaphytosis of the feet. No idea as to dosage is known. In 1944, he developed extensive ulceration over the lateral border of the right foot. Sixteen bi-weekly treatments with 200 e.s.u. radon ointment for 24 hours were entirely ineffective. Skin grafting is to be done.

CASE 17. A white female, aged 35. This patient had a full dose of superficial Roentgen ray therapy for a plantar wart in 1940. When the plantar wart recurred, another series of Roentgen ray therapy was given. The resulting ulcer never healed and in May 1943, when treatment was started, there was a 0.5 x 1.5 cm. ulcer on the sole of the foot. Twenty weekly treatments with 100 e.s.u. radon ointment applied for 8 hours were a failure. Complete excision and skin grafting was done in November 1943, with a good result.

Results of Treatment. From January 1943 until August 1945, 17 cases of late radiation necrosis were treated with radon ointment in the Department of Radiology of this hospital. One of these patients (Case 2) had a recurrence of his ulceration 18 months later, while another patient (Case 5) developed a second ulcer in another previously irradiated area. Of the 19 ulcers thus treated, 12 healed completely, 2 showed a good response but failed to heal completely, while 5 showed little or no response. The 2 cases (Cases 7 and 12) which showed a good response but failed to heal completely were known to have proven carcinoma remaining in the lesion when therapy was instituted. Both had inoperable carcinoma that had been subjected previously to heavy irradiation.

Discussion. Our favorable results with this method of treatment, while not as uniformly successful as those achieved by Uhlmann,[13,14] lead us to believe that his introduction of alpha particle therapy is a new approach and a definite advance in the non-surgical treatment of what has heretofore been a very discouraging clinical problem. While our experience with the problem has been quite limited compared to Uhlmann's, we have been able to follow our cases quite carefully and to satisfy ourselves that radon ointment shows promise of occupying a definite place in our therapeutic armamentarium.

One of the most striking features in its use was the prompt relief of pain when combined with methods for control of the concomitant infection. The change in the mental outlook of the patient was most gratifying to the observer. Definite evidence of healing has been noted in some 1 week after institution of treatment. Such early response augurs for rapid and complete recovery, and the repair process, once begun, may continue even though the radon ointment is no longer applied.

TABLE 2.—ANALYSIS OF DATA

Case No.	Underlying condition	Site of ulcer	Radon ointment applications*	Response	Remarks
1	Epithelioma 6670 r (June 1942)	Dorsum of hand (January 1945)	200 e.s.u. twice a week for 12½ wks.—24 hrs. per treatment	Healed in 16 wks.	Ulcer 3 cm. in diameter
2	Epithelioma 1200 mg. hrs. contact radium, 2 mm. brass, 1550 r (July 1930)	Dorsum of hand (*a*) January 1943	(*a*) 100 e.s.u. for 8 hrs., once a week for 10 wks.	(*a*) Healed in 10 wks.	Keratotic horn followed healing of first ulcer; 16 mos. later another ulcer developed
		(*b*) October 1944	(*b*) 200 e.s.u. for 24 hrs., twice a week for 20 wks.	(*b*) None	
3	Epithelioma 8000 r (February 1939)	Dorsum of hand (October 1942)	100 e.s.u. for 8 hrs., once a week for 1 yr.	Slight	Radiation necrosis and fracture of metacarpal at base of ulcer; granulations appeared after fracture
4	Eczema Dose unknown (1928 and 1929)	Dorsum of finger (1940)	100 e.s.u. for 8 hrs., once a week for 27 weeks	Slight	
5	Hyperthyroidism Dose unknown (1939)	Neck (1943)	(*a*) 100 e.s.u. for 8 hrs., once a week for 5 wks.	(*a*) Healed in 5 wks.	1.5 cm. ulceration, second ulcer appeared 6 wks. later, following scratching
			(*b*) 100 e.s.u. for 8 hrs., once a week for 11 wks.	(*b*) Healed in 11 wks.	
6	Hyperthyroidism 12,000 r (1933 to 1934)	Neck (March 1945)	200 e.s.u. for 8 hrs., once a week for 8 wks.	Healed in 12 wks.	Complicated by urticaria in treated area; this was shown to be due to extraneous factors
7	Basal cell carcinoma 7500 r (1940)	Neck (1941) (February 1943) (October 1943)	Sulfonamide ointment 100 e.s.u. for 8 hrs., once a week for 15 wks.—repeated 6 mos. later	Good at first; no response later	3 ulcers—2 with residual malignancy—all healed at first but 2 with residual malignancy recurred
8	Epithelioma 9000 r (November 1941)	Inner canthus of eye (February 1943)	100 e.s.u. for 8 hrs., once a week for 3 wks.	Healed in 3 wks.	Ulcer, 1.5 cm. in diameter
9	Basal cell carcinoma 487 mg. hrs. radium (March 1941) 9000 r (June 1941)	Outer canthus of eye (January 1943)	100 e.s.u. for 8 hrs., once a week for 3 wks.	Healed in 3 wks.	Ulcer 1 cm. in diameter
10	Epithelioma 6300 r (July 1940), 3900 r (August 1940)	Upper lip (January 1942)	100 e.s.u. for 8 hrs., once a week for 5 wks.	Healed in 6 wks.	Ulcer 0.75 x 1 cm.; patient not seen until December 1942
11	Epithelioma 2500 r (January 1939), 4300 r (April 1944), 1900 mg. hrs. radium	Nose and cheek (January 1945)	200 e.s.u. for 24 hrs., once a week for 24 wks.	Healed in 24 wks.	
12	Carcinoma 1400 r to each of 3 20 x 20 portals (June 1943)	Breast (April 1944)	200 e.s.u. for 24 hrs., twice a week for 12 wks.	Good	Residual carcinoma present; large deep ulcer almost completely filled in, due to treatment
13	Experimental irradiation 3200 r (September 1942)	Anterior thigh (December 1943)	100 e.s.u. for 8 hrs., once a week for 19 wks.	Healed in 20 wks.	Ulcer, 1 x 2 cm.
14	Experimental irradiation 3500 r (August 1942)	Anterior thigh (March 1944)	200 e.s.u. for 12 to 24 hrs., twice a week for 25 weeks	Healed in 26 wks.	Ulcer, 1 x 2 cm.
15	Neurogenic sarcoma 6000 r (1932)	Leg (1943)	200 e.s.u. for 48 hrs., twice a week for 4 wks.	Healed in 6 wks.	Ulcer, 1 x 1.5 cm.; patient not seen until April 1945
16	Dermatophytosis Dose unknown (1937–1938)	Foot, lateral border (1944)	200 e.s.u. for 24 hrs., twice a week for 8 wks.	None	
17	Plantar wart Dose unknown (1940)	Foot, plantar surface (May 1943)	100 e.s.u. for 8 hrs., once a week for 20 wks.	None	Subsequently removed surgically

* 100 e.s.u. = 40 microcuries. 200 e.s.u. = 80 microcuries.

In some instances, however (Cases 11 and 14), persistence over a long period of time was rewarded by disappearance of the ulcer. A favorable response to therapy is manifested by increased vascularity in the previously avascular ulcer bed where slight trauma, such as removing fibrinous exudate, will produce bleeding. One may observe the appearance of small capillaries or exuberant granulations at the periphery of the ulcer. In some cases, however, the changes are quite minimal and the repair process is insidious. In 2 of our cases (Cases 5 and 6) complaint of pruritus was soon followed by healing.

Apparently any area of the body is amenable to treatment. It should be noted that most of our failures have occurred on the hands and on the feet. This may be related to the question of diminished blood supply, vascular stasis, lack of adequate connective tissue stroma, or possibly neurotrophic factors.

Meticulous care in the control of infection, eradication of slough, and the cleansing and dressing of a wound may yield gratifying results in what appears at first glance to be a hopeless situation. Case 12 had been heavily irradiated elsewhere, for what was an inoperable carcinoma of the breast. She subsequently developed a deep indolent foul-smelling ulcer in the anterior axillary fold. The surgeons refused to perform a palliative simple mastectomy because of the ulcer, and she was referred to our department for treatment. For a period of about 4 weeks she received daily applications of zinc peroxide paste, followed subsequently by sulfallantomide ointment. At the time of her death, due to metastases, the ulcer had almost completely healed, despite the presence of residual malignancy in the breast.

While we have encountered no untoward effects from the treatment with radon ointment, its potential dangers should be appreciated, both for the physician and the patient. On testing normal individuals, it has been noted that a definite skin erythema was produced in 8 hours in some cases.[8] Thus, it behooves the physician to avoid contact with a material to which he may be exposed many weeks in the year. When not in use, the material should be stored under lead protection for detectable gamma radiation has been observed by us by the use of appropriate instruments such as the Geiger counter and the Victoreen minometer.

Summary. 1. Seventeen cases presenting 19 late irradiation ulcers were treated with a new therapeutic agent—radon ointment.

2. Twelve of the ulcerations showed complete healing in a period ranging from 3 to 50 weekly applications.

3. Two lesions having residual malignancy showed a good response but failed to heal completely.

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ADDISON'S DISEASE IN THE NEGRO

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From the very small number of case reports which can be found in the literature one gains the impression that the occurrence of Addison's disease in the Negro is extremely rare. This conclusion is somewhat surprising since the incidence of tuberculosis (one of the major causes of destruction of the adrenal glands) is greater in Negroes than in whites. That one is not justified in using the total number of cases reported in the literature as an index of the rarity of a disease seems obvious. If one assumes that the occurrence of Addison's disease in the Negro is far greater than would be indicated by the 21 cases reported in medical literature of the world since 1907, one may speculate: (1) that many cases so diagnosed have seemed to be of insufficient interest to warrant their being reported; (2) that physicians who make the diagnosis are unaware of the paucity of reported cases; or (3) that the disease appears to be rare in Negroes because the diagnosis is usually missed. We believe that all 3 have contributed, but that the third is the reason of greatest importance. It is easily understandable that when dealing with Negro patients the possibility of Addison's disease would suggest itself less frequently than in the case of whites, since pigmentation of the skin is usually one of the most striking manifestations of the disease. Because we feel that it is timely that this problem be brought to the attention of the practicing physician we are adding 5 of our own cases to those already reported.

The first case of Addison's disease in a Negro was reported by Scheult,[5] in 1907. Lisa, Solomon and Gordon[2] reviewed the literature on this subject in 1942 and found 17 reported cases. They added 3 of their own. From then to the present time no additional cases have been described, but Shipley[7] in reporting upon the therapeutic efficacy of pellets of desoxycorticosterone acetate mentions that 1 patient in his group was a Negro.

Our group consists of 3 patients recently seen by us on whom the clinical diagnosis was made, and of 2 on whom the diagnosis was made at postmortem examination some years ago (the clinical diagnosis was suspected in 1 of these).

Case Reports. Recognized Clinically. Case 1. J. R., a 42 year old male Negro, was admitted to the University Hospital on Oct. 7, 1943, complaining of severe weakness, anorexia, nausea and vomiting, chronic cough and pain in the right shoulder. These symptoms had begun 2 years previously and had been gradually progressive. Over this period the patient had lost 70 pounds of body weight (200 to 130 pounds). He stated he had noticed increased pigmentation over the dorsum of the hands, the elbows and the nipples. On the initial examination he was found to be drowsy and lethargic. The blood pressure in the supine position was 80/58. There were large irregular patches of pigmentation on the dorsum of the tongue (up to 1.5 cm. in diameter). Marked pigmentation of the gums, palate and buccal mucosa was present.

Laboratory studies revealed a plasma NaCl of 403 mg. %, N.P.N. 45.5 mg. %, fasting blood sugar 52 mg. %, and a water test[4] markedly positive in both phases. The urine was negative and there was a moderate hypochromic anemia.

A good rise in blood pressure and gain in strength followed 3 days of treatment with desoxycorticosterone acetate (D.C.A.) and

NaCl. On the 5th day he developed chills and fever with clinical and Roentgen ray evidence of a right basal pneumonitis. Lethargy, asthenia and hypotension returned. Recovery followed intensive therapy with saline, glucose and adrenal cortical extract intravenously; D.C.A. and adrenal cortical extract intramuscularly; and sulfadiazine orally. He was discharged on 3 mg. D.C.A. daily, apparently well (B.P. 115/80), having gained 11 pounds in weight.

On 2 subsequent occasions he has been hospitalized for the treatment of infection (upper respiratory infection in 1944 and osteomyelitis of a finger in 1945). On each of these admissions the findings of acute adrenal cortical insufficiency were present and responded to adequate therapy.

Repeated sputum concentrates and cultures have been negative for acid-fast organisms. The Congo red test was negative.

At present the patient weighs 197 pounds and is doing full time light work without undue fatigue. His blood pressure has been stabilized at about 135/80 with the use of 3 mg. of D.C.A. daily. He takes a high carbohydrate diet (without salt supplement) which includes a late evening feeding.

CASE 2.—E. H., a 50 year old male Negro, was admitted to the University Hospital on Oct. 20, 1944, complaining of weakness and vomiting. His symptoms had begun about 1 year before, during which interval he had lost 45 pounds in weight. For 1 month prior to admission his asthenia had progressed to the point of virtual complete prostration. Both he and his family volunteered the information that his skin had become darker over the past few months.

Examination revealed a man who appeared much older than his stated age and who spoke in a very feeble voice. The blood pressure was 80/50. The skin was that of a dark Negro. There was marked pigmentation of the mucous membranes of the mouth. Large, irregular patches of pigmentation covered most of the dorsal surface of the tongue.

Laboratory studies showed a plasma NaCl level of 485 mg. %, N.P.N. of 41.5 mg. %, 17-ketosteroid excretion of 3.1 mg. per day and a water test[4] markedly positive in both phases. Chest Roentgen ray showed no evidence of active pulmonary disease. On admission, the blood showed a hemoglobin of 113% with 5.9 million R.B.C. per c.mm. After hydration these levels were found to to be 89% and 4.6 millions respectively. The urine was essentially negative.

After 4 days of treatment with desoxycorticosterone acetate and salt, appetite began to return and the blood pressure stood at 125/80. There was a gratifying symptomatic response. He was discharged after 31 days of hospitalization feeling well and strong, having gained 10 pounds in weight (without evidence of edema) with a B.P. of 120–130/70–80, and taking a daily maintenance dose of D.C.A. When he had failed to return for reëxamination 2 months after discharge, it was discovered that he had died in another city. On discharge, he had not been given sufficient D.C.A. to last for 2 months. No *autopsy* had been done and little information could be obtained regarding the circumstances of his death.

CASE 3.—V. M., a 36 year old Negress, was admitted to the University Hospital on Sept. 10, 1942, with complaints of weakness, weight loss, anorexia, nausea and backache. These symptoms had begun in mild form 3 years previously and had gradually progressed. Weight had dropped from 189 to 115 pounds over this period. A hysterectomy had been done elsewhere 1 year before admission. The weakness and gastro-intestinal symptoms had increased markedly in severity since her operation.

Examination revealed an emaciated, dehydrated Negress who showed evidence of chronic illness. The blood pressure was 100/65. No other physical abnormalities were observed. Complete gastro-intestinal Roentgen rays showed 10% gastric retention in 6 hours. Gastroscopy revealed only atrophic gastritis. Chest Roentgen ray was negative. Pelvic examination was likewise negative. There was a moderate hypochromic anemia. Urine was negative. The water test[4] was strongly positive in both phases. A persistent daily elevation of temperature to 100° to 101° F. was present throughout the hospital stay. This was associated with a white blood cell count varying from 6000 to 10,000 per c.mm. Miliary tuberculosis was suspected but not confirmed clinically.

The patient remained in the hospital for only 9 days of therapy for adrenal cortical insufficiency. Although a rise of blood pressure to 120/80 occurred, clinical improvement was not impressive. The lack of a

more rapid response to specific therapy was believed to have been due to the presence of toxicity, the cause of which remained obscure. She was instructed in the use of D.C.A. (5 mg. intramuscularly daily), 3 gm. of supplementary NaCl daily and a high carbohydrate diet. It is doubtful that she followed instructions.

One month later she died at another hospital. It was the impression of the attending physician that she died in Addisonian crisis. *Autopsy* was not performed.

Diagnosed Pathologically. CASE 4. F. L., a 22 year old male Negro, admitted on the Dermatological Service of the University Hospital on Nov. 20, 1924. Died on December 23.

Clinical diagnoses: sacrofuloderma, pulmonary tuberculosis and latent syphilis.

Pathologic diagnoses: generalized amyloidosis, with virtually complete replacement of adrenal cortices by amyloid. Tuberculous osteomyelitis of vertebræ (Pott's disease with psoas abscess). Disseminated miliary tubercles in lymph nodes. Serofuloderma. "Addison's disease."

CASE 5. J. C., 60 year old male Negro, admitted on the Medical Service of the University Hospital in a moribund condition on Dec. 5, 1925. Died the following day.

Clinical diagnosis: miliary tuberculosis, Pott's disease, chronic fibroid pulmonary tuberculosis.

Pathologic diagnosis: "Addison's disease." Bilateral chronic caseating tuberculosis of adrenals with very little adrenal tissue remaining. Chronic pulmonary tuberculosis. Generalized miliary tuberculosis (pleura, peritoneum, lungs, heart muscle, liver, spleen, kidneys and lymph nodes). Tuberculous necrosis of third, ninth, tenth and eleventh thoracic vertebræ. Pott's disease.

Discussion. Although changes in the degree of pigmentation of the skin may be difficult to evaluate in some Negroes, the triad of asthenia, gastro-intestinal symptoms (anorexia, nausea, vomiting and diarrhea) and hypotension should suggest the possibility of adrenal cortical insufficiency. Having thought of this possibility one may be aided further by inquiring about any recent increase in the degree of pigmentation of the skin. Two of our most recent patients volunteered the information that their skins had definitely become darker in recent months, particularly over the forehead, the dorsum of the hands, the elbows and about the nipples. In 1 case this had been noted by the family before the patient was admitted for treatment. Since patchy pigmentation of the buccal mucous membranes occurs physiologically in a large proportion of Negroes, this sign (an important supplementary criterion in whites) is of little significance. We have been impressed, however, by the presence of large areas of pigmentation on the dorsal surface of the tongue. While Monash[3] reports that some degree of pigmentation on the dorsal surface of the tongue may be found in 33% of normal Negroes, the intensity of this finding in the 2 patients who had noted increased pigmentation of the skin, tempts us to relate it to the adrenal insufficiency. Sodeman[8] and his staff at Charity Hospital in New Orleans where 55% of admissions are Negroes inform us that in their experience obvious pigmentation on the dorsum of the tongue of normal Negroes is extremely rare.

Incidence of Addison's Disease in Negroes. There are several points of interest which militate against the apparent rarity of Addison's disease in the Negro race. Thorn[10] and Blankenhorn[1] have seen a number of cases which have not been reported. Both feel that the majority of cases go unrecognized. Eight unreported cases have been diagnosed at Charity Hospital.[8] Sturgis has seen at least 1 unreported case.[9] It is clear that a thorough survey designed to disclose unreported cases would, relatively speaking, skyrocket the total number of cases which have been recognized; this despite the fact that the majority have undoubtedly gone unrecognized.

The problem of clinical *versus* pathologic diagnoses throws additional light on the question of the difficulty of clinical recognition. Sodeman reports[8] that of 4 cases in which there was no doubt of the final diagnosis, 3 were diagnosed at autopsy and only 1 was recognized clini-

cally. Of the 21 cases found in the literature, 12 were diagnosed clinically and 9 were discovered at postmortem examination. In the 12 cases diagnosed clinically, the average duration of symptoms before diagnosis was 16.8 months, the average duration of life after diagnosis being 2.3 months. It should be suggested parenthetically, that the relatively good showing of clinical *versus* pathologic diagnoses as determined from the literature may be more apparent than real. Failures in diagnosis are less likely to be reported than successful diagnoses. Of our own group of 5 cases, 3 were diagnosed clinically and 2 at autopsy. Thus, the high percentage of initial diagnoses made at postmortem means that we are missing the clinical diagnosis too frequently. How many times such an undiagnosed Negro patient fails to come to postmortem examination must remain purely speculative, but whatever the number is, it adds to our clinical failures and to the total number of unsuspected cases. There may be some hope in the fact that of the 21 cases reported in the literature from 1907 to 1944, 11 have been reported in the last 8 years.

Of 78 cases of Addison's disease observed at the University Hospital, the 5 reported above have occurred in Negroes (a ratio of 15.6 white cases to 1 Negro case). Of the total registration figures at this hospital, about 1.7% are Negroes. Thus the ratio of whites to Negroes is 58.8 to 1. If these figures were to be taken seriously, they would mean that Addison's disease occurs about 4 times more frequently in Negroes than in whites, registered at this hospital. The figures suggest, at least, that Addison's disease is as common in the Negro as in the white race.

Sex Incidence. The total incidence of well-grounded diagnoses of Addison's disease of all races in the 420,500 registrations at the University Hospital from 1925 to 1944 is 0.019%. Of the 78 cases in all races 59% were males and 41% were females. Among the 26 cases in Negroes reported in the literature and by us, 65% have been in males and 35% in females.

Etiology of Addison's Disease in the Negro. Over the past 10 years an impressive change has occurred in the etiologic incidence of Addison's disease in the white race. Whereas tuberculosis of the adrenals formerly comprised 80 to 90% of all cases examined pathologically, the diagnosis of idiopathic adrenal cortical atrophy has gradually increased in recent years so that it has now assumed the No. 1 position among the various causes of adrenal insufficiency, being variously reported as occurring in 40 to 60% of all cases. Our own experience in this regard is summarized in Table 1 and is compared with data now available in the literature with regard to Negroes.

TABLE 1

All cases autopsied	No. cases	Tbc.	Cortical atrophy	Amyloidosis	Syphilis
U. of M., 1900–1934 (all races)	17	11 (65%)	2 (12%)	3 (17%)	1 (6%)
U. of M., 1935–1945 (all races)	11	6 (55%)	5 (45%)	0	0
Negroes (entire literature), 1907–1945	20	19 (95%)	0*	1 (5%) U. of M.	0

* We are informed that 1 unreported case seen recently by Sheldon and Howes[6] showed idiopathic cortical atrophy at postmortem examination. This occurred in a young male Negro soldier in the European Theatre of Operations.

Of particular interest is the highly significant fact that of 7 cases of idiopathic adrenal cortical atrophy observed in whites at the University Hospital over a period of 45 years, 5 have occurred over the past 10 year period. Speculation in this connection is beyond the purpose of this report.

That *all* of the cases heretofore reported in Negroes have been due to tuberculosis is, at least, somewhat surprising.

Summary. Five cases of Addison's disease in Negroes are described. This brings the total number of reported cases to 26. There is undoubtedly a much greater number of recognized cases which have not been reported. Probably the largest increment of cases of Addison's disease in Negroes is not being recognized as such. It is extremely doubtful that the incidence of Addison's disease in Negroes is smaller than in whites. Analysis of our own cases leads to the opposite conclusion.

Increased pigmentation of the skin, the most striking hint that the physician may be dealing with Addison's disease in whites, is frequently of little or no value in suggesting this possibility as he examines the Negro patient. If, however, he does think of this possibility, retrospective information from the patient with regard to increased pigmentation of the skin may be helpful. In addition to the usual cardinal signs and symptoms of adrenal insufficiency marked pigmentation on the dorsal surface of the tongue may be a significant finding.

All of the cases reported in the literature upon which a pathologic examination was made were found to be due to tuberculosis of the adrenals. One of our cases was due to amyloidosis of the adrenals giving a total etiologic incidence on all 20 autopsied cases of 95% for tuberculosis and 5% for amyloidosis. From the information at hand it would appear that idiopathic atrophy of the adrenal cortices (which now accounts for about 50% of all cases in whites) is either non-existent or extremely rare in the Negro. This is probably not a valid conclusion.

Conclusion. Physicians must be on guard for the recognition of Addison's disease in the Negro, which is in all probability much commoner than the number of reported cases would indicate.

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USE OF AN AGGLUTINATION INHIBITION TEST IN STUDYING THE EFFECTS OF VACCINATION AGAINST INFLUENZA

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A readily available method for measuring influenzal antibodies is based upon the inhibition by convalescent or immune sera of the agglutination of chicken and certain other red blood cells in the presence of influenza viruses. A modification of Hirst's[9] original agglutination-inhibition (A–I) technique was described by one of us 2 years ago, together with an account of its use in studying an epidemic due to influenza Type A.[5] The present communication is to report some observations made with this test following vaccination against influenza Types A and B.

Attempts have been made to produce active immunity to influenza with specific vaccines ever since ready sources of these viruses became available.[6,10,19] Although the early results were not very satisfactory, they tended to indicate that height of specific antibody level and protective immunity were proportional, and that the more virus present in a vaccine the better it was as an immunizing agent. The most promising one yet to be made available on a large scale was a concentrated preparation containing 2 Type A strains (PR–8 and Weiss) and 1 Type B (Lee). The viruses were concentrated from allantoic fluids of embryonated eggs and killed with formalin. This vaccine was studied extensively by the Influenza Commission of the United States Army during 1943 and 1944.[4,7,8,11,12,14,17] Over 6000 students were vaccinated at 8 colleges scattered throughout the country. An equal number at each of these institutions was studied as controls. The antibody response to the vaccine was comparable to that produced by natural infection and almost all those vaccinated developed an increase in A–I antibodies for both PR–8 and Lee. Individuals with higher pre-vaccination titers tended to show relatively smaller increases. Peak titers were reached by 2 to 3 weeks. When sera were obtained and re-tested after 3 to 4 months, a 15 to 30% fall in antibody level was noted. In a subsequent Type A epidemic approximately 2.5 times as many cases occurred among the controls as among the vaccinated, an incidence of 8.3% in contrast to 3.3%. The poorest results were obtained when the vaccine was given about 6 weeks before the start of the epidemic,[4] then 4% of those vaccinated and 6% of the controls developed influenza. The best results were shown when the vaccine was not given until after the epidemic had already started. At one such institution[11] only 1.7% of those vaccinated became ill in contrast to 8% of the controls. There was definite protection by the end of 1 week.

In the fall of 1945, in the face of a rising incidence of influenza, mostly due to a Type B virus, the Army directed that this vaccine be administered to all of its personnel. Although the subsequent rapid demobilization of military installations interfered with original plans for a large scale coöperative study of this mass immunization by this and 2 other laboratories in this area, it was possible for us to follow a local group carefully and to carry out the studies which are the subject of this report.

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Materials and Methods. *Study Group.* Adequate information and sera were available from 89 individuals. Of these, 30 were members of this laboratory staff and the remaining 59 were corpsmen at a nearby Army hospital. Their average age was 20 to 30 years.

Vaccine. Influenza Virus Vaccine Types A and B. Refined and Concentrated (Lederle—Lot No. 2031–27A) was used. Each subject was given 1 ml. subcutaneously in the deltoid region.

Sera. Blood specimens were collected at the time of vaccination and again after 1 and 3 weeks. Each serum was separated and withdrawn shortly after collection and stored in the refrigerator in vials containing sulfanilamide as a bacteriostatic agent.

Agglutination-Inhibition Test (A–I) Test. The modified Hirst A–I technique reported earlier from this laboratory[5] was used throughout. All specimens from an individual were tested at the same time. Known positive sera were always included. If the titers obtained with these controls differed by more than one dilution, the tests were repeated. Only 4-fold or greater rises in antibody were considered significant. The PR–8, Weiss and Olson (Type A) strains and the Lee (Type B) strain were obtained from Dr. M. D. Eaton (State Virus Laboratory, Berkeley, California). The Saha (Type B) strain was received from Lt. M. M. Sigel (5th Service Command Laboratory, Fort Benjamin Harrison, Indiana).

Records. At the time of vaccination each subject was questioned in regard to recent influenza, previous respiratory infections, and allergy to egg protein. The members of the laboratory staff who were in the study were interviewed 24 and 72 hours after vaccination. The others were questioned in regard to reactions to the vaccine at the time the 1 week post-vaccination specimen of serum was collected. The subjects on the laboratory staff were instructed to report to one of us with all subsequent illnesses. In those instances which clinically resembled influenza, throat washings, and acute and convalescent phase sera were collected for study. Approximately 12 to 14 weeks later follow-up interviews were held with slightly more than half of the entire group.

Plan of Study and Results. *Relation of Type of Reaction to Vaccine to Pre-vaccination A–I Antibody Level.* Beveridge and Burnet[1] while studying the effects of intradermal inoculation of influenza viruses observed that allantoic fluids infected with influenza virus A or B produced a cutaneous reaction in most adults and in some children. In these children it was usually associated with the corresponding type of circulating antibody. This suggested to us that reactions following the subcutaneous administration of influenza vaccine might be similarly related to already present antibody. To investigate this possibility, the reactions experienced by our subjects were analyzed in terms of each individual's pre-vaccination titer of specific A–I antibody.

Approximately two-thirds of the study group complained of an untoward reaction within 4 to 24 hours following vaccination. Although the kinds of reactions experienced were similar to those previously reported with this vaccine, their distribution was quite different. Fifteen (17%) developed only local reactions; 34 (38%) complained only of systemic symptoms ranging from transient malaise to fever lasting 6 to 24 hours; and 9 (10%) had both local and systemic signs and symptoms. None required hospitalization. Thirty-one (35%) did not complain of any reaction. We followed the classification used by Eaton and Meiklejohn,[4] and yet the 17 and 38% (or including combined reactions, the 27 and 48%) of our 89 subjects who experienced local and systemic reactions respectively are very different from the 31 and 23% of their 116 with such complaints. Other observers have reported still different distributions. Rickard, Thigpen and Crowley[14] found that 91% of 550 college students had local and 18% had generalized symptoms. Some of these differences may be a reflection of the manner of questioning the subjects, but it is difficult to account for the majority. It was hoped therefore that serologic analysis would yield pertinent information. In Table 1 there are the results of testing the pre-vaccination sera of the individuals in the group classi-

TABLE 1.—RELATION OF IMMEDIATE REACTIONS TO VACCINE TO INITIAL ANTIBODY LEVELS AND TO SUBSEQUENT ANTIGENIC STIMULATION

		Pre-vaccination A–I antibody levels									Changes in antibody level 3 weeks after vaccination (Fold increase over original titer)								
		PR 8			Weiss			Lee			PR-8			Weiss			Lee		
Reaction to vaccine	No. persons	<8–16	32–128	256+	<8–16	32–128	256+	<8–16	32–128	256+	0–2	4–16	32+	0–2	4–16	32+	0–2	4–16	32+
None	31 (35%)	20	11	0	25	6	0	22	8	1	8	23	0	10	21	0	7	17	7
Local	15 (17%)	6	9	0	11	4	0	12	3	0	10	3	2	6	7	2	2	9	4
Systemic	34 (38%)	25	9	0	28	6	0	20	14	0	17	14	3	13	20	1	7	21	6
Combined	9 (10%)	6	3	0	8	1	0	8	1	0	4	5	0	2	7	0	1	7	1
	—	—	—	–	—	—	–	—	—	–	—	—	–	—	—	–	—	—	—
Totals	89 (100%)	57 (64%)	32 (36%)	0	72 (81%)	17 (10%)	0	62 (70%)	26 (29%)	1 (1%)	39	45	5	31	55	3	17	54	18
												50 (56%)			58 (65%)			72 (81%)	

fied according to reaction to the vaccine. Unfortunately, no fundamental differences are apparent except in regard to PR–8 antibody among those who had local complaints. However, there were only 15 individuals in this group. It would seem therefore that except for this one possibility, which must be studied further, there is no relation between an individual's prevaccination titer and the likelihood of his experiencing an untoward reaction from the vaccine.

Table 1. Relatively fewer of those who experienced local symptoms developed 4-fold or greater rises in antibody titer for PR–8. However, as already noted, this group had proportionately more individuals with higher initial levels for this virus. These results are therefore compatible with the observation that increase in A–I antibody titer following infection or vaccination tends to be inversely proportional to initial antibody level. Similar consideration of the other groups failed to reveal

TABLE 2.—REPRESENTATIVE VARIATIONS IN ANTIBODY RESPONSE TO VACCINE

	Weeks after vaccination	A			B	
		*PR–8**	*Weiss*	(Olson)	*Lee*	(Saha)
No. 513	0	<8	<8	<8	16	<8
	1	128	64	16	128	32
	3	1024	512	128	256	128
Profile†	..	+	+	+	+	+
No. 235	0	16	32	8	16	8
	1	64	64	32	64	32
	3	64	64	32	128	256
Profile	..	+	−	+	+	+
No. 236	0	<8	<8	<8	<8	<8
	1	8	8	8	8	8
	3	8	32	16	512	128
Profile	..	−	+	+	+	+
No. 522	0	32	8	8	<8	<8
	1	128	16	8	8	<8
	3	256	64	32	16	8
Profile	..	+	+	+	+	−
No. 531	0	8	32	8	16	<8
	1	8	32	8	32	8
	3	16	64	16	128	64
Profile	..	−	−	−	+	+
No. 241	0	32	16	8	16	16
	1	32	32	16	32	32
	3	32	32	16	32	64
Profile	..	−	−	−	−	+
No. 215	0	8	32	32	16	32
	1	16	64	64	32	32
	3	16	64	64	32	32
Profile	..	−	−	−	−	−

* Virus strains in italics are those contained in the vaccine.
† "Profile" represents pattern of significant changes in A–I antibody levels produced by vaccination.

Relation of Reaction to Vaccine to Antigenic Stimulation. To investigate the possibility that the capacity for antigenic stimulation by the vaccine might be related to the immediate reaction it elicits in an individual, the changes in A–I antibody 3 weeks after vaccination were compared for each of the groups indicated in any correlation between reaction and increase in A–I antibody. The reactions of those who at the end of 3 weeks had attained an A–I titer of 1:256 for one or more of the viruses in the vaccine were then analyzed separately. There were 37 individuals with such high levels. Among this group of good antibody pro-

ducers there were 13 (35%) without any reactions, 5 (14%) with local, 15 (40%) with systemic, and 4 (11%) with combined reactions. Although this represents only 42% of the entire study group, the distribution of reactions is strikingly similar to that shown in Table 1.

Relation of Pre-vaccination History to Initial A–I Antibody Levels. In an attempt to find an explanation for the considerable variation in pre-vaccination A–I titers, our data were analyzed in terms of the histories of upper respiratory infections obtained at the time of vaccination. There were 31 who reported having frequent upper respiratory infections and 9 who gave a history of having had influenza during the preceding 2 years. But among the former 31 there were 20 (64%) initial A–I antibody titers of 1:16 or less for PR–8, 25 (81%) for Weiss, and 20 (64%) for Lee. Among the 9 with histories of recent influenza there were 6 with such low levels for PR–8, 6 for Weiss, and 5 for Lee. This distribution is almost identical with that for the study group considered as a whole (Table 1).

Rickard, Thigpen and Adams[15] while studying influenza Type A in 5 infants found that the acute phase A–I titers ranged between 1:26 and 1:79. Since these infants were too young to have been exposed to a previous influenza epidemic, they suggested that the base line titers might represent non-specific inhibiting substance similar to that found in the serums of some normal laboratory animals. It is entirely possible that some of the lower pre-vaccination titers found in our adults were also of this nature. Nevertheless, despite our inability to correlate them with influenza or respiratory infections which the subjects recalled, most of the higher pre-vaccination titers probably still reflected previous clinical or sub-clinical influenzal infections.

Time of Appearance of Antibodies. Since it had been reported[8,11] that this vaccine gave significant protection by the end of 1 week against infection by a Type A virus, we attempted to determine the time of appearance of increase in the several A–I antibodies it elicited. There were 86 individuals from whom pre-vaccination, 1 and 3 week post-vaccination serum specimens were available. Analysis of our data suggests that the A–I antibodies for Type A tend to appear earlier than those for Type B. Thirty-two (37%) attained their highest level for a Type A strain in 1 week, while only 21 (24%) did this for the Type B virus. Of those reaching their peak titer in 1 week for only 1 strain there were 17 (20%) for Type A, and 6 (7%) for Type B.

Relation of 3 Week Post-vaccination A–I Titers to Incidence of Subsequent Respiratory Infections. Between 11 and 14 weeks after vaccination it was possible to interview 52 of the group in regard to their general well-being. Thirty-three reported no respiratory illnesses while 19 complained of having had "colds." Eight said that they had had more "colds" than during the preceding 5 years. Yet 11 of the 19 with histories of subsequent respiratory illnesses produced A–I titers of 1:256, or above, for 1 or more of the viruses within 3 weeks after vaccination, while only 9 of the 33 who did not develop upper respiratory infections developed such high antibody levels. Although the majority of these infections was probably not influenza, we did have 2 serologically proven instances due to a Type B virus among the 30 individuals in the laboratory. Both of these illnesses were associated with low grade fever, malaise and leukopenia and were in men who had not produced high levels of B antibody after vaccination. The results of testing their pre-vaccination, post-vaccination, acute and convalescent phase sera against the Lee virus are contrasted in Chart 1 with those of another subject who was sick at about the same time with an illness later diagnosed as "bronchitis."

Effect of Vaccination on Serologic Test for Syphilis. Since no information was available as to the effect of this vaccine and the resultant increase in A–I antibodies on a serologic test for syphilis,

Lt. Annis Wilkerson, WAC, kindly examined 2 or more sera from 59 of these subjects in the standard Kahn flocculation test. By 3 weeks, when the great majority of false positive reactions following smallpox vaccination are noted,[13] none had shown any change.

Antigenicity of the Vaccine. When the 3 week post-vaccination sera were compared with those obtained at the time of vaccination, a 4-fold or greater rise in antibody was found for at least one of the component antigens in 83 (93%) of the study group. There were 55 individuals for PR–8 3 weeks after vaccination, 65% for Weiss and 81% for Lee. It was also found that whereas only 9 individuals attained post-vaccination titers of A–I antibody of 1:256, or greater, for PR–8 and for Weiss, there were 31 with such levels for the Lee virus.

One of the most important considerations for any vaccine is the broadness of the antibody response it stimulates. Although the specificity of influenza viruses is less evident with human sera than with those from animals, it is well established that a satisfactory vaccine for clinical use

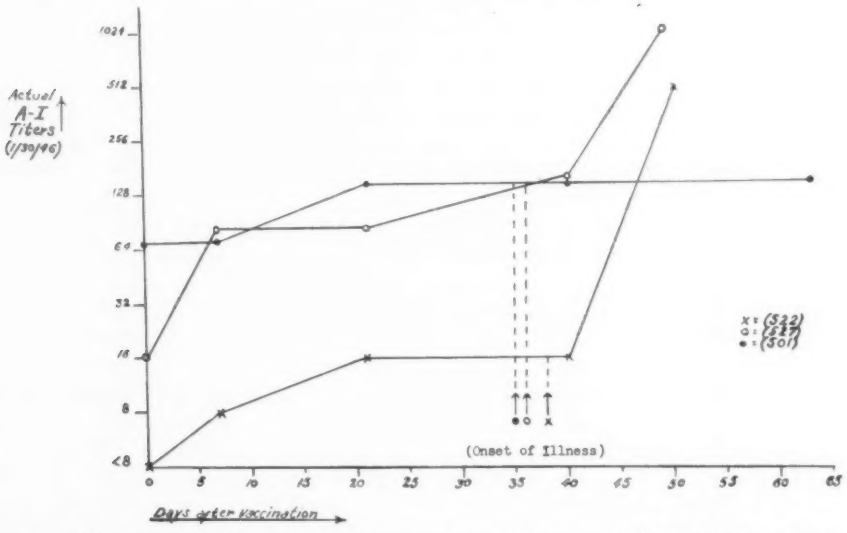

CHART 1.—Effect of vaccination and subsequent respiratory illness on A–I antibody for Type B (Lee) influenza.

(62%) who developed significant increases for both a Type A and the Type B strains. Eighteen (20%) showed such a rise for the Type B virus alone and 10 (11%) did so only for a Type A strain. There were just 6 (7%) in whom the vaccine failed to elicit any significant rise in antibody.

We have no data available as to the actual amount or distribution of specific influenza virus protein in the vaccine. However, if one accepts the resultant A–I titers as indications of antigenicity, interesting results are obtained. In Table 1 it is shown that 56% of the entire group had 4-fold or greater rises in A–I antibody

must contain both A and B strains. It is perhaps not so well recognized that there are definite antigenic differences among individual members within these types. However, it was this that prompted the inclusion of the Weiss Type A strain, which had been isolated in Michigan early in 1943,[16] in the vaccine along with the well-established laboratory strains, PR–8 and Lee.

In order to examine the vaccine in respect to this broadness of antigenicity, we subjected the sera from our groups to A–I tests against 2 recently isolated influenza viruses. As a representative of

Type A the so-called Olson strain was obtained from Dr. M. D. Eaton who had isolated it from a patient in California during the fall of 1943.[4] The Saha, Type B, strain was obtained from Lt. M. M. Sigel who had isolated it during an outbreak at Camp Atterbury, Indiana, in the spring of 1945.[18]

Type B. It shows that in general the pre-vaccination antibody for the 2 A strains which are in the vaccine (PR–8 and Weiss) and for the test strain (Olson) are quite similar. However, the antigenic stimulation for Olson is less striking than for either of the other 2 strains. There were 9 individuals who attained levels of

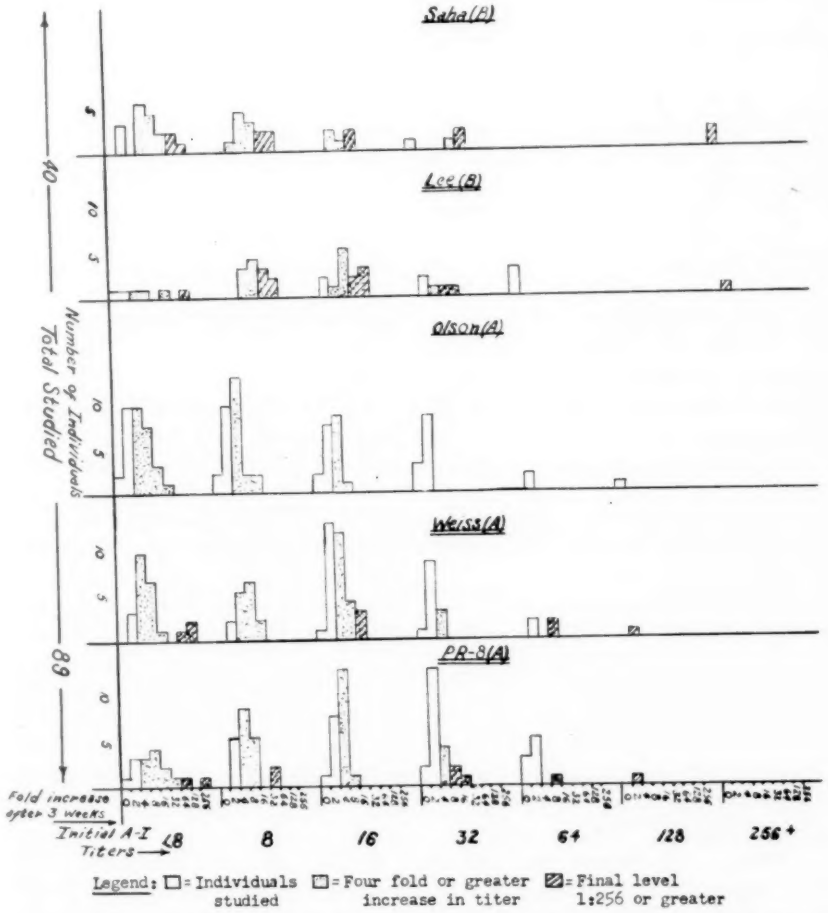

CHART 2.—Comparative antigenicity of components of vaccine.

In Chart 2 there is summarized for comparison the titers obtained at the time of vaccination and the antibody increases evoked by vaccination. Such comparative data was available for 89 individuals for the Type A strains and for 40 of the

1:256 or greater for PR–8 and for Weiss, but none who did so for Olson. In contrast both the pre- and post-vaccination levels for the Lee and the test strain (Saha) are quite similar. There were 14 individuals who attained post-vaccination

levels of 1:256 for Lee and 13 for Saha. It would seem that either the Saha strain is antigenically more nearly like the Lee than the PR–8 and Weiss are like the Olson, or that the antibody response evolved by the Lee virus is not only quantitatively greater, as has already been shown, but also is immunologically broader than either of the A strains in the vaccine.

Individual Variations in Response to Antigens. As has already been indicated, there were marked differences in the manner in which individuals responded to this vaccine. Some produce significant increases in antibody for all of the components, while others did so for only certain ones. There were even a few who did not apparently respond to the antigens administered but did demonstrate 4-fold, or greater, increase in antibody when tested against the Olson or Saha strains. In Table 2 there are listed a few representative types of response by individuals all of whom initially had low A–I titers. If the amount of circulating A–I antibody produced is proportional to an individual's protection against infection, this variability of immunologic response is a serious failing of the present vaccine.

Discussion. The all important question of whether this vaccine protects against an epidemic of influenza due to a Type B virus could not be answered because of the limitations imposed by the size and nature of the study group. However, with the aid of the A–I test it was possible to gather immunologic data and to attempt a correlation with clinical observations.

It is perhaps significant that the 2 proven instances of Type B influenza were in men who had failed to develop high levels of antibody for the B component of the vaccine. These unpredictable responses present a difficult problem.

Every comprehensive study of human antibody response to an immunizing agent has uncovered a proportion of individuals who develop little antibody and there were a few such non-reactors in our group. Effective immunization against influenza is probably impossible for them.[3] Our data also indicates that there are individuals who respond only to certain parts of the mosaic of antigens which make up an influenza virus so that they subsequently may have higher levels of antibody for related viruses than for those used as antigens. A similar phenomenon has been reported in enteric fever.[2] In some instances, especially early in the disease, the agglutination titer with the homologous Salmonella is much lower than with a related type. The effect of this kind of reaction on protection against future influenzal infections is not yet known. It awaits further study.

Summary. 1. Immunologic data were obtained with the aid of an agglutination-inhibition (A–I) test from 89 individuals who had been given a concentrated influenza virus vaccine containing 2 Type A (PR–8 and Weiss) strains and 1 Type B (Lee).

2. This information was analyzed in relation to clinical observations associated with the administration of the vaccine.

3. Almost two-thirds of the group complained of either local or systemic reactions shortly after vaccination. However, these symptoms did not seem to be the result of an antigen-antibody reaction involving A–I antibody since the distribution of pre-vaccination levels of antibody was in general similar among those who did not have such complaints as among those who did. Neither was it possible to associate an individual's immediate reaction to the vaccine with his subsequent production of antibodies.

4. Two serologically proven instances of Type B influenza infection occurred during the 5th week following vaccination. Both were in men who had not produced high levels of antibody for the B component of the vaccine.

5. A–I antibodies for the Type A viruses tended to appear earlier than for Type B. There were 17 individuals (20%) who reached their peak level for a Type A strain only at 1 week, but just 6 (7%) who did so for the Type B.

6. Administration of the vaccine and the resultant changes in A–I antibodies did not change the Kahn flocculation serologic test for syphilis reagin titer in the 59 individuals so studied.

7. By 3 weeks after vaccination, 83 (93%) of the group had developed 4-fold, or greater, rises in antibody for at least 1 component of the vaccine. There were 56% who did so for PR–8, 65% for Weiss and 81% for Lee. Although only 9 individuals attained titers of 1:256 for PR–8 and for Weiss, 31 did so for Lee.

8. The sera were also tested against recently isolated Type A and Type B viruses (Olson and Saha) in order to study the broadness of antibody response. The results indicated that either the Saha strain is antigenically more nearly like the Lee than the PR–8 and Weiss are like the Olson, or that the antibody response evoked by the Lee virus is immunologically broader than that of the A strains in the vaccine.

9. Individual variations in serologic response to the vaccine were striking. Among those who responded there were some who did so to all of the components of the vaccine, some who did so only to certain ones, and a few who did not produce antibodies to the viruses in the vaccine as well as they did for the related Olson and Saha strains. The unpredictability of this phenomenon presents a serious problem if the level of circulating A–I antibody produced is indicative of the amount of protection against infection afforded by a vaccine.

The technical assistance of Sgt. Fred Trader, Miss Frances Condie and Mr. John Long was helpful in completing these studies. The charts were photographed by the U. S. A. Signal Corps.

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THE ELECTROCARDIOGRAPHIC EFFECTS OF PROSTIGMIN*

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Tachycardia remains a difficult problem therapeutically and often interferes with the proper evaluation of the myocardial status in the interpretation of the electrocardiogram. Removal of the cause of the increased heart rate is to be recommended, but frequently, no cause is found. Recently, reports[3,4,5] have appeared extolling prostigmin for all forms of tachycardia, including: simple or sinus; paroxysmal, ventricular or supraventricular, whether functional, organic or idiopathic. If this material is effective for the purposes recommended, it deserves wider use, not only as a therapeutic measure, but, as a diagnostic aid, since, electrocardiographically, a more accurate appraisal of the myocardium should be possible through slowing of the rate. The following report is based upon the study of 42 patients, appraising the effectiveness of this drug.

Material and Method. Patients selected for study were from private practice and from the cardiac clinic of The Chicago Medical School. The types of conditions present may be seen in Tables 1 and 2. The ages of the patients varied between 11 and 75 years, with a fairly even distribution between the ages of 20 and 70 years. There were 15 males and 27 females.

The patients were not informed of the intent of the study. They were conducted through the experiment as though it was the usual electrocardiographic technique employed. After a short rest period, the usual leads were taken. Then classical Lead 2 was retaken while 2 ampoules of 1:2000 prostigmin methylsulfate† solution (1 mg.) were administered subcutaneously. The time of the injection was marked upon the film by a standardization. A short strip of film (Lead 2) was taken at 5 minute intervals at 5, 10, 15, 20, 25 and 30 minutes after the injection, the patient remaining in recumbency.

Results. The effect of prostigmin upon the rate of the heart measured electrocardiographically may be seen in Table 1. In this table the patients are classified according to the clinical diagnosis. It is noted that in no instance was the rate increased, whereas, in 26 (62%) the rate was slowed 20 or more beats per minute, and in 10 (24%) the rate was slowed between 10 and 20 beats per minute. The heart rate remained unchanged or was decreased less than 10 beats per minute in 6 (14%) of the patients.

The greatest effect was usually noted in the tracing taken 20 minutes after the injection. Occasionally, the most marked slowing was noted at 15 minutes, while some individuals showed the greatest slowing after a 25 minute interval. However, this variation was slight and for practical purposes, one tracing taken after 20 minutes should give the average major response obtainable. Usually, the rate increased slightly after 25 minutes, and this tendency became pronounced at the 30 minute interval, indicating the short duration of the effect of the drug.

When the effect of prostigmin upon the cardiac rate was measured according to the electrocardiographic classification (see Table 2), again it may be noted that in no instance was the rate increased, regardless of the mechanism present. Using the slowest rate obtainable (usually at the

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† The material used was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

20 minute period), 86% showed a slowing of 10 beats per minute or more. Frequently this was over 40 beats per minute. In 6 instances there was no effect upon the rate: namely, sinus mechanism in a patient with hyperthyroidism undergoing treatment with thiouracil; 2 instances of sinus tachycardia in patients with untreated hyperthyroidism; paroxysmal auricular tachycardia in a patient with hypertensive heart disease; paroxysmal ventricular tachycardia in a patient with a myocardial infarct; and, auriculoventricular heart block in a patient with allergy, who frequently complained of rapid heart action, but when the test was done the rate before the injection was only 70 beats per minute.

There were several changes noted in the form of the electrocardiogram in addition to a decrease in the rate. Examples are shown in Figure 1. In 2 individuals with sinus tachycardia the P waves became inverted during the height of the effect of the drug. This result was evanescent and frequently may have been missed. In 1 instance (hyperthyroidism, Fig. 1 *D*), the P wave was inverted only at the 20 minute interval; in the other example (neurocirculatory asthenia, Fig. 1 *E*), the P wave inversion was noted only at the 15 minute interval.

The P–R interval was uninfluenced by the drug except in 1 instance of neurocirculatory asthenia in which the P-R was reduced from 0.18 to 0.16 second. In 1 case of rheumatic heart disease the P–R interval was increased from 0.16 to 0.18 second. In Figure 1 *B*, it is difficult to

TABLE 1.—EFFECT OF PROSTIGMIN UPON THE HEART RATE OF 42 PATIENTS CLASSIFIED ACCORDING TO CLINICAL DIAGNOSIS

Clinical diagnosis	No. patients	Rate slowed 20/min. or more	Rate slowed 10 to 20/min.	Rate slowed less than 10/min.	Rate increased
Neurocirculatory asthenia	14	8	6	0	0
Hyperthyroidism	6	3	0	3	0
Rheumatic heart disease	7	5	2	0	0
Hypertensive heart disease	6	4	1	1	0
Arteriosclerotic heart disease	1	1	0	0	0
Coronary artery disease	3	2	0	1	0
Miscellaneous:					
Allergy	1	0	0	1	0
Alcoholism	1	1	0	0	0
Abscess of leg	1	1	0	0	0
Thyroid extract poisoning	1	1	0	0	0
Idiopathic	1	0	1	0	0
Total number	42	26	10	6	0
Per cent	100	62	24	14	0

TABLE 2.—EFFECT OF PROSTIGMIN UPON THE HEART RATE OF 42 PATIENTS CLASSIFIED ACCORDING TO ELECTROCARDIOGRAPHIC DIAGNOSIS

Electrocardiographic diagnosis	No. patients	Rate slowed 20/min. or more	Rate slowed 10 to 20/min.	Rate slowed less than 10/min.	Rate increased
Sinus mechanism	4	2	1	1	0
Sinus arrhythmia	4	1	3	0	0
Sinus tachycardia	21	15	4	2	0
Paroxysmal auricular tachycardia	3	2	0	1	0
Paroxysmal ventricular tachycardia	1	0	0	1	0
Auricular fibrillation	5	4	1	0	0
Auricular flutter	2	2	0	0	0
Left bundle branch block	1	0	1	0	0
Auriculoventricular block	1	0	0	1	0
Total number	42	26	10	6	0
Per cent	100	62	24	14	0

measure the P–R interval before the drug was administered because of the fusion of the P and T waves. This becomes much more clearly defined after the injection; since there is remarkable constancy of this measurement throughout the series, there is no reason to assume much change in this example of first-degree heart block.

In 2 instances of sinus tachycardia the QRS complexes became heightened as the rate decreased, although this effect was minor. The QRS complex was increased in amplitude when the mechanism changed from supranodal tachycardia to sinus tachycardia (Fig. 1 *H*) in a patient with an acute myocardial infarct. The paroxysm stopped 2 minutes after the injection of prostigmin when the patient vomited. It was impossible to state that the drug was responsible for arresting this

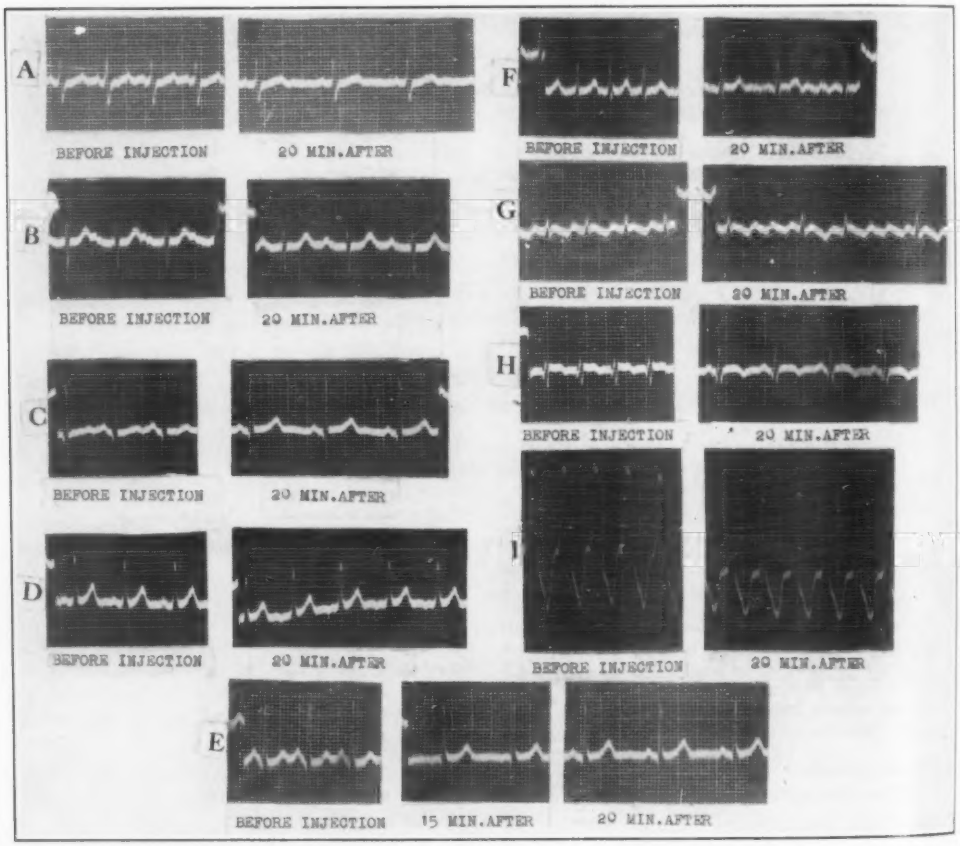

FIG. 1.—All tracings shown are classical Lead 2 before and 20 minutes after injection of 1 mg. of prostigmin methylsulfate. *A*, Note the marked slowing which resulted (125 beats to 74 beats per minute) in a case of thyroid extract poisoning.[2] *B*, Hypertensive heart disease: the slowing after injection permitted accurate appraisal of the prolonged auriculoventricular conduction time. *C*, Note increase in height of the T waves 20 minutes after injection. The rate was slowed. Clinical diagnosis: abscess of leg. *D*, Inversion of the P waves without slowing of the rate in a case of hyperthyroidism. *E*, Transitory P wave inversion at 15 minutes which has returned to normal at the 20 minute interval. The rate was decreased in this case of neurocirculatory asthenia. *F*, In a case of arteriosclerotic heart disease with auricular fibrillation, the ventricular rate was markedly slowed after the injection of prostigmin. *G*, In a case of hypertensive heart disease the previously regular 2:1 auricular flutter became irregular, increasing the block. *H*, The heart rate slowed abruptly 2 minutes after injection. The mechanism (supranodal tachycardia postmyocardial infarction) reverted to a sinus tachycardia and the amplitude of the QRS was increased. *I*, The rate during an attack of paroxysmal ventricular tachycardia (after a myocardial infarct) was uninfluenced by the injection of prostigmin.

attack, since a subsequent paroxysm was not aborted similarly.

The T waves increased in amplitude in 4 instances of sinus tachycardia. The clinical diagnoses were: abscess of leg (Fig. 1 *C*) hyperthyroidism, neurocirculatory asthenia, and rheumatic heart disease. The rate was unaffected in paroxysmal ventricular tachycardia but the T waves were more definite in form. This is apparent, although the difficulties of standardization may have been responsible for some of this effect.

The ventricular rate was slowed in 5 cases of auricular fibrillation (Fig. 1 *F*), and in 2 cases of auricular flutter (Fig. 1 *G*).

Discussion. The most pronounced effect of the injection of 1 mg. of prostigmin methylsulfate was upon the cardiac rate, which was slowed in 86% of the cases. While this slowing may have been as small as 10 beats per minute, yet a similar result could not be obtained with any other method: namely, carotid sinus pressure, rest, sedation, etc., when, and at the time this effect was desired, and according to electrocardiographic measurement.

Waldman and Moskowitz[4,5] reported that the drug had no effect upon "constant tachycardia" associated with definite disease, but Bram[1] has refuted this. In our 6 cases of hyperthyroidism the sinus tachycardia was slowed in 3. Of the 3 cases unaffected, 1 had been treated with thiouracil and the tachycardia was no longer present. Of course, the effect was only temporary, tending in all instances to return to the earlier increased level after the 30 minute interval. This agrees with the findings of Waldman and Moskowitz.

Pelner[3] reported the increased effectiveness of carotid sinus pressure in conjunction with prostigmin in restoring the normal rhythm in cases of paroxysmal tachycardia. No such effect was noted in our 3 instances. While the paroxysm stopped in 1, the result came so soon after the injection (2 minutes) that it would be impossible to ascribe the cessation of the attack to the drug. The rate was decreased in the other 2 cases, but the attack was not stopped either with the drug alone or with the energetic application of carotid sinus pressure.

The effects of the drug orally were disappointing. Prostigmin bromide (15 mg.) tablets were administered. The rate was not slowed as dramatically and the deceleration achieved by the subcutaneous route could not be maintained by the use of the oral preparation. When a dosage large enough to produce notable slowing was used orally the unpleasant side-effects became so marked that only rarely could the drug be tolerated.[4] It had been hoped that following an injection the oral preparation could be used with better therapeutic effect. This result was not achieved.

The side-effects encountered usually had passed off within a 2 hour period after an injection. The symptoms consisted of nausea, abdominal pains, twitching of the eyelids, tightness of the skeletal musculature of the jaws producing a speech difficulty and giddiness. These were more alarming in the group classified as neurocirculatory asthenia, but in no case severe enough to warrant the use of the antidote, atropine sulfate.

Most of the effects upon the form of the electrocardiogram are explained upon the basis that the rate is slowed by stimulation of the parasympathetics. This slowing permitted a more normal contour of the T wave to appear in 4 instances of sinus tachycardia. This effect probably also accounts for the occasionally noted increase in the QRS amplitude. No explanation is offered for the transitory inversion of the P waves.

For future work an electrocardiogram using classical bipolar and multiple unipolar leads will be compared before, and 20 minutes after the injection. The method followed in this series has established that the 20 minute period will permit the recording of the maximum change produced. When multiple leads are compared in this manner, clues to the myocardial state will undoubtedly become more apparent, justifying the procedure

as a test in selected cases. This, in effect, constitutes a reversal of the well-known electrocardiographic effect of proving nutritional insufficiency by increasing the heart rate by lowered oxygen tension or exercise tests.

Summary and Conclusions. 1. The effects of 1 mg. prostigmin methylsulfate upon the electrocardiograms of 42 patients were observed.

2. The cardiac rate was slowed in 86% of the patients studied, including both organic and functional conditions.

3. Besides a decreased rate, other effects were noted, including transient inversion of the P wave, increase in amplitude of the QRS, increase in the amplitude of the T waves, separation of a fused T and P wave in auriculoventricular block, slowing of the ventricular rate in auricular fibrillation and auricular flutter.

4. The effect of the oral preparation of prostigmin bromide was disappointing when used therapeutically.

5. The procedure recommended is to compare complete electrocardiograms before and 20 minutes after the injection.

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THE TOXIC EFFECTS OF PROLONGED INGESTION OF DDT* ON DOGS WITH SPECIAL REFERENCE TO LESIONS IN THE BRAIN

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Tremor followed by incoördination, muscular twitching, flaccidity, and other manifestations of impairment of the central nervous system have been observed in a variety of animals given DDT (Cameron and Burgess,[2] Draize, Nelson and Calvery,[4] Lillie and Smith,[6] Neal and associates,[7,8] Orr and Mott,[10] Smith and Stohlman,[12] Nelson and Calvery[14]). Similar symptoms, lasting for months, developed in a man subsequent to inunction of an acetone solution of DDT (Wigglesworth[13]). The literature contains 2 reports on the clinical manifestations of DDT intoxication in dogs. Nelson and associates[9] observed tremor in 2 dogs given a total of 2.8 gm./kg. of DDT in corn oil by stomach tube for 1 month, and in a third which received 10.5 gm./kg. of DDT in the same manner for 7 months. Draize, Nelson and Calvery[4] found that animals displayed no ill effects throughout 9 months during which they received by inunction a total of 0.3 to 1.2 gm./kg. of a 30% solution of DDT in dimethyl phthalate. The clinical and certain of the pharmacologic aspects of DDT intoxication in 28 dogs, from 4 of which many of the data for our study have also been gathered, have been reported by Bing, McNamara and Hopkins.[1]

Studies of the central nervous systems of animals after administration of DDT have yielded little of note. Cameron and Burgess[2] gave a total of 0.8 gm./kg. of DDT to rabbits over a period of 16 days, and 1.5 gm./kg. to rats for 30 days (the DDT in each instance being suspended in liquid paraffin and tragacanth and administered by stomach tube). Degenerative changes took place in anterior horn cells of the spinal cord but not in the cerebrum, cerebellum or brain stem. Lillie and Smith[6] had much the same experience with cats, rabbits and rats. Complete lack of change in the central nervous system of a variety of animals, including the dog, was reported also by Nelson and associates.[9]

Of the pathologic changes in the thoracic and abdominal viscera, the most notable have been in the liver. These consisted either of (1) centrolobular cytoplasmic oxyphilia or hyaline degeneration or (2) centrolobular and midzonal fatty degeneration progressing to focal or zonal necrosis or to atrophy. The only change observed in the kidney was that of fatty degeneration of tubular epithelium, usually mild to moderate in degree. It is apparent from the various reports in the literature that visceral lesions occurred only after the administration of relatively large amounts of DDT.

Methods. The dogs given DDT and those used as controls for our study were chosen at random from the kennels at Edgewood Arsenal. All were mongrels, most of them females; they were from 1 to 4 years old, and weighed from 6.1 to 18 kg. All were on an ample diet supplemented by vitamins and were in excellent health before the experiment was started.

Eight dogs comprised the experimental series. They were given a solution of 10% DDT in peanut oil by stomach tube in doses ranging from 150 to 350 mg./kg. The prepa-

* 2, 2-bis (p-chlorophenyl)-1,1,1-trichloroethane.

ration was given daily except when the systemic reaction brought about by previous dose was excessive; sometimes several days elapsed before use of the preparation was resumed. When the animals were too ill to eat, no attempt was made to force-feed them. There were 9 controls; 5 untreated, 2 which received peanut oil by stomach tube for 90 days in an amount equivalent to that used as a solvent for the DDT given in experimental animals (3 cc./kg. daily), and 2 which were given peanut oil and subsequently fasted until they lost 20 and 31% of their body weight respectively.

Four of the animals given DDT died, and the remainder, as well as the controls, were sacrificed by means of intracardiac injections of 10 cc. of nembutal. All of the autopsies were done promptly. The brain, spinal cord and samples of the sciatic and vagal nerves were fixed in 10% formalin, and blocks of the thoracic and abdominal viscera in Zenker's solution. The eyes of 2 of the experimental animals and of 1 of the controls also were fixed in 10% formalin. After fixation, the cerebrum was sectioned in the coronal plane at 7 representative levels, the brain stem at 3, the cerebellum at 3, and the spinal cord at 4. The material was embedded in paraffin. The sections of the brain and spinal cord were stained routinely with cresyl violet and those of the viscera and the eyes with hematoxylin and eosin. In certain instances, frozen sections from the central and peripheral nervous systems were stained for fat by scarlet red, for myelin by the Spielmeyer method, and for axis cylinders by the Bodian method.

Clinical Observations.* In general, the symptomatology varied in accordance with the amount of the daily dose of DDT. Large doses given for a few days usually induced more severe symptoms than smaller doses over a prolonged time. Tremor constituted the earliest manifestation of DDT intoxication. Initially it was fine, generally starting in muscles of the eyelids and face and spreading with variable sequence and severity to all muscles. The tremor occurred spontaneously when the animals were at rest, but was accentuated by excitement or movements, being most intense on completion of a movement. On daily doses ranging from 150 to 200 mg./kg. the tremor usually did not develop until several days had elapsed, but sometimes became apparent after the first dose; it began 4 to 6 hours after DDT had been given, generally lasted for several hours, and remained reversible after prolonged administration. Three examples in this category are listed in Table 1 (Nos. 133115, 159669 and 159668).

When, however, the daily dose of DDT ranged from 180 to 250 mg./kg., or higher, the course was one of steady decline. Anorexia, listlessness and weakness set in, weight loss occurred in 4 (Table 1), and eventually death occurred. Tremor developed after the first administration of DDT and except for 1 instance (No. 159673), became more coarse and widespread than in animals given a lower daily dose. Moreover, the animals (Nos. 147733, 147732, 159672 and 135777) became ataxic and developed hypermetria, which, together with the tremor, ultimately became irreversible. On standing, such animals were unsteady, and their limbs usually were hyperextended and abducted. They tended to stagger when walking, lifted their legs unduly high with each step, and often were unable to arrest locomotion, with the result that they bumped into clearly visible objects. After a time the stretch reflexes of the limbs became overactive; thus, when the head was thrust backward the tone of the forelimbs was considerably augmented, and when the head was tilted to the right or the left the hindlimb of the corresponding side underwent extreme extension. Also the placing reactions were strongly positive, *i. e.*, when the animals were held in the air with eyes shielded to occlude vision, the slightest contact of the anterior aspect of a paw with the edge of a table resulted in an exaggerated flexion of the limb, followed by maximal extension. No disturbance of sensibility was detected, nor were

* The clinical observations herein described were made jointly by Bing, McNamara and Hopkins[1] and ourselves.

TABLE 1.—THE DOSAGE OF DDT AND THE APPROXIMATE DEGREE OF DEGENERATION OF THE CEREBELLAR NUCLEI

AIP dog No.	Av. range of daily dose (mg./kg.)	No. doses	Total dose (gm./kg.)	Period over which DDT was given (days)	Period of survival (days)	Severity of neurologic symptoms*	Weight loss (%)	Died or sacrificed	Cell counts of the cerebellar nuclei in 30 low power fields (× 100) and the degree of degeneration				
									Total cells	Normal cells	"Abnormal cells"†	"Abnormal cells"† %)	Degeneration (%)
147733	250–300	40	7.46	103	110	++++	27	S	1901	973	928	48.8	36.9
147732	200–250	42	7.16	98	99	+++	0	D	1875	718	1157	61.7	49.8
159672	300–350	21	5.40	28	28	+++	0	D	2130	1440	690	32.4	20.5
135777	180–250	14	2.46	17	18	+++	18	S	2508	1926	582	23.2	11.3
133115	150–200	21	3.74	24	25	++	0	S	2415	1948	467	19.3	7.4
159669	150–200	9	1.70	13	13	++	14	D	1925	1655	270	14.0	0
159673	300–350	21	5.95	28	28	+	44	D	2655	2378	277	10.4	0
159668	150–200	10	1.90	13	13	+	0	S	2605	2314	291	11.2	0
						Untreated Controls							
153842	...	..	...	...	...	...	0	S	2042	1744	298	14.6	0
153843	...	..	...	...	..	...	0	S	2253	1985	268	11.9	0
153844	...	..	...	...	...	..	0	S	2218	1974	244	11.0	0
153845	...	..	...	...	...	...	0	S	2501	2190	311	12.4	0
153846	...	..	..	..	...	...	0	S	2308	2082	226	9.8	0
						Peanut Oil—Treated Controls							
159671	...	..	...	...	90	...	16	S	2680	2366	324	12.1	0
159670	...	..	...	...	90	...	0	S	2132	1815	315	14.8	0
						Peanut Oil—Treated and Fasted Controls							
162957	...	..	...	...	90	...	31	S	2690	2501	189	7.0	0
167958	...	..	...	...	90	...	20	S	2520	2274	246	8.4	0

* Irreversible symptoms are indicated by 3+ and 4+, reversible ones by 1+ and 2+.

† A sharp line of distinction between faded and actually degenerated cells could not be made—hence the grouping together of all cells not having a normal appearance.

there defects of vision or hearing. None of the animals had convulsive seizures.

The 2 dogs given peanut oil by stomach tube over a period of 90 days had no untoward symptoms, and appeared to be as healthy at the termination of the experiment as at the beginning; 1 lost 16% of its body weight, while the other gained an equivalent amount. Lack of symptoms was also apparent in the other 2 controls so long as peanut oil was given; when, in addition, they were fasted they lost weight but otherwise suffered no visible untoward effects.

Gross inspection of the brain and leptomeninges of the dogs given DDT revealed moderate congestion and occasional petechial hemorrhages. The ventricles appeared to be of normal size. Microscopic examination revealed nothing of significance in the cerebrum, brain stem, peripheral nerves, or eyes. At all levels of the spinal cord, there was a normal complement of anterior horn cells but some of them displayed slight to moderate chromatolysis.

The cerebellum showed varying degrees of damage. In animals in which the level

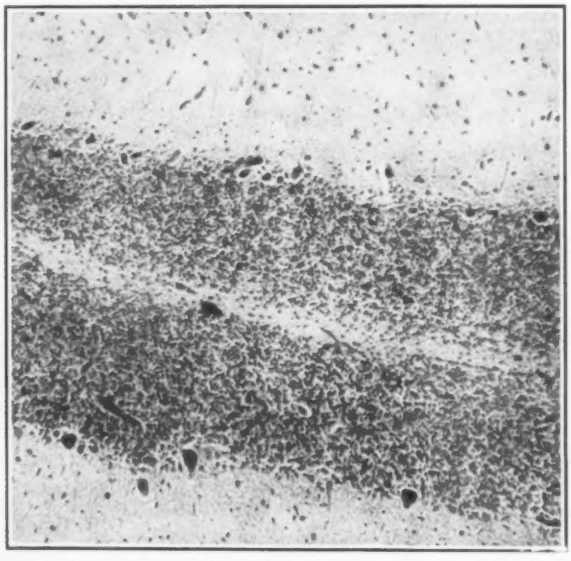

FIG. 1.—(Dog 147732; total dose of DDT, 7.16 gm./kg.). Many of the cells of the cerebellum are shrunken and otherwise distorted, and a few have disappeared. The molecular, Bergmann, and granular layers show nothing of significance. (Cresyl violet, × 145.) (AIP neg. 90295.)

Pathologic Anatomy. Examination of the thoracic and abdominal viscera of the animals receiving DDT revealed constant lesions only in the liver. The most characteristic of these consisted of sinusoidal engorgement in association with fatty degeneration of hepatic cells, usually centrolobular in distribution but sometimes midzonal as well. Hemosiderosis of Küpffer cells and centrolobular atrophy were observed in some of the cases of longer standing. No significant changes were found in the other tissues.

of dosage of DDT ranged from 150 to 200 mg./kg. a moderate number of Purkinje cells exhibited swollen and hyperchromatic cytoplasm and pyknotic nuclei to a degree not observed in the controls. The dentate and roof nuclei, however, were not convincingly abnormal except in 1 instance (No. 133115) in which mild degeneration was apparent (Table 1). Moderate to severe degenerative change in the cerebellum was observed in all animals given 180 to 350 mg./kg. of DDT, except in 1 instance (No. 159673). In 2

of the animals receiving the largest doses over the greatest length of time (Nos. 147733 and 147732) many of the Purkinje cells were pyknotic or had been converted into "ghosts," and a few had disappeared (Fig. 1). There was no hyperplasia of cells of the Bergmann and molecular layers, nor were changes detected in the granular layer. The dentate and roof nuclei were severely affected. As compared to a section from a control (Fig. 2), the nerve cells were somewhat fewer in number, and many of those remaining displayed chromatolysis and vacuolization of the cytoplasm, and karyorrhexis or complete loss of nuclei; some cells were completely amorphous (Figs. 3 and 4). There was no generalized gliosis but the number of satellite glia was sometimes increased (Fig. 3).

An effort was made to determine quantitatively the degree of degenerative change in the dentate and roof nuclei. This was done by counting the number of normal and abnormal cells in 3 low power fields (100 × magnification) of the 10 serial sections, making a total of 30 fields examined; the fields chosen were those in the mid-portion of the dentate nucleus of both sides and the fastigial nucleus of one side. The small aggregation of cells corresponding to the emboliform nucleus of man was also examined. Care was taken to cut all sections at 6 microns. At a later date the counting was repeated, and the average of the 2 counts taken as the final figure. Cells exhibiting mild chromatolysys or slight blurring of nuclear detail were included among the normal forms; those so hazy that cellular detail could not

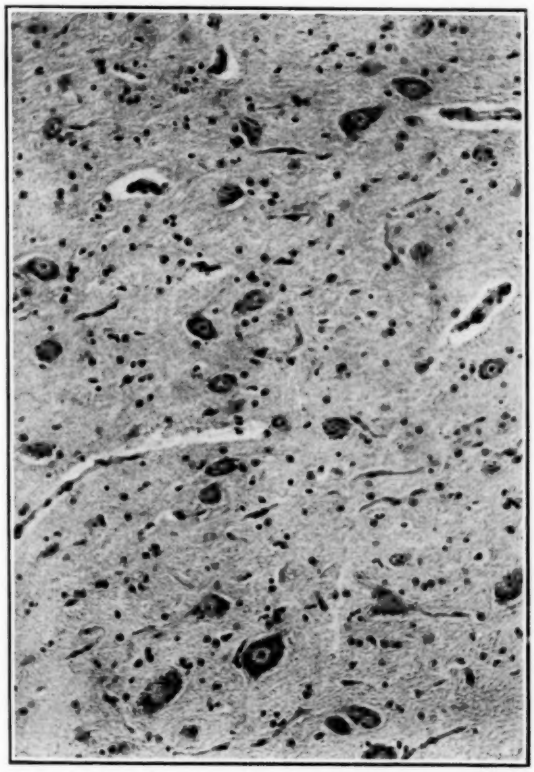

FIG. 2.—(Dog 153846; untreated control.) The ganglion cells in this field of the dentate nucleus are numerous and virtually all of them have the features of normal cells. (Cresyl violet, × 230.) (AIP neg. 92211.)

be discerned and those obviously degenerated were listed as abnormal. The results, which are to be regarded as only approximate, are shown in Table 1. Abnormal forms in the untreated controls varied from 9.8 to 14.6%, and averaged 11.9%. (The abnormalities were ascribed to postmortem change or to artefact.) Approximately the same degree of alteration was observed in the controls receiving peanut oil and in the animal which had been fasted. In 4 of the animals in which the daily dose of DDT ranged from 180 to 350 mg./kg. (Nos. 147733, 147732, 159672 and 135777), and 1 in which the daily dose range was 150 to 200 mg./kg., a moderate to marked increase in the number of abnormal cells was found. The figures on the over-all degeneration of this group, which varied from 7.4 to 49.8%, were obtained by subtracting the average % "abnormal cells" in the 5 untreated controls (11.9 %) from the % "abnormal cells" found in each of the dogs treated with DDT. Statistically evaluated, the index of nuclear degeneration in the first 6 animals listed in Table 1 were as follows: 20.7, 27.9, 11.5, 6.3 4.2, 1.2. The amount of cell destruction in the animals given DDT was not significantly large, but what there was, could be correlated with the total doses given, the value of the correlation coefficient being 0.76.

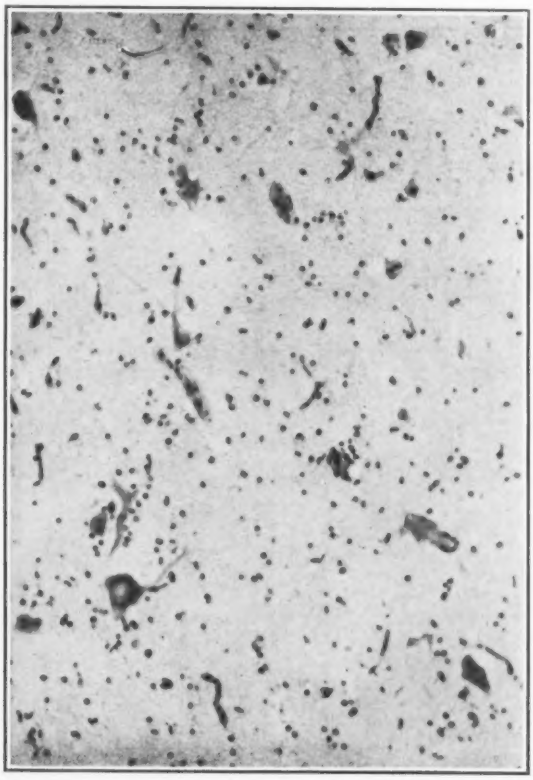

FIG. 3.—(Dog 147732; total dose of DDT, 7.16 gm./kg.) This field of the dentate nucleus contains 6 relatively normal cells and numerous faded or obviously degenerated forms. As compared to the control (Fig. 2), the actual number of cells is not greatly reduced. Satellites in the vicinity of 1 of the distorted cells are increased in number. (Cresyl violet, × 250.) (AIP neg. 92266).

Discussion. From the clinical standpoint it seemed apparent that the severity of the symptoms depended more on the

amount of daily dose of DDT than on the total dose. Thus, Dog 135777 received a daily dose of from 180 to 250 mg./kg. DDT, amounting altogether to 2.47 gm./kg., and developed irreversible symptoms, whereas Dog 133115, on a smaller daily dose but a greater total dose was not affected clinically to the same degree. That tolerance to DDT varies is indicated by the failure of irreversible symptoms to develop in Dog 159673 despite high daily and total doses; judging by the loss of weight, this animal exhibited the most severe systemic reaction of the group. Two animals (Nos. 147733 and 147732) receiving large daily doses of DDT over the longest period had the most striking neurologic symptoms and the greatest degree of degenerative change in the cerebellum. The data on the entire series would seem to indicate that damage to cells of the cerebellum is slowly progressive and probably irreparable.

The lack of changes in other portions of the central nervous system points to the cerebellum as the essential site of action of DDT. This view is supported by the observation that the symptoms displayed by dogs given DDT over an extended period of time were strikingly similar to those observed by Fulton and Dow[5] and Rademaker[11] in decerebellated dogs. Consistent with this view also are the results of a study by R. J. Bing* on cats in which the spinal cord and brain stem were sectioned prior to the adminis-

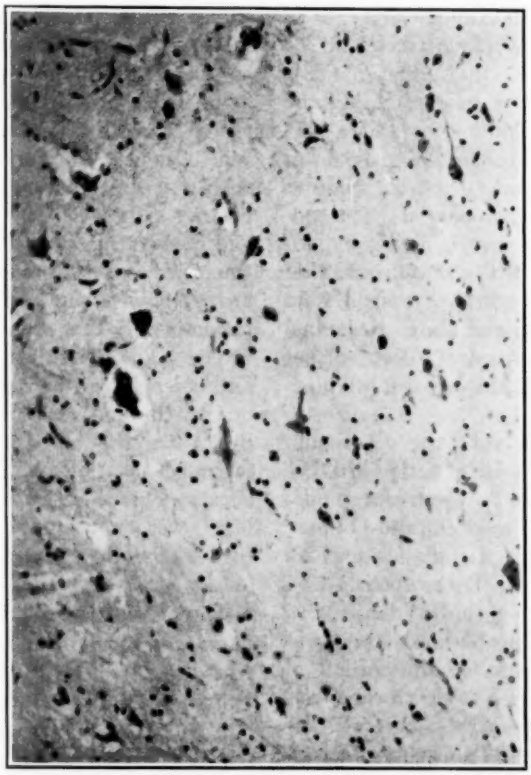

FIG. 4.—(Dog 147733; total dose of DDT, 7.46 gm./kg.) This also is a field of the dentate nucleus showing a preponderance of shriveled and otherwise distorted cell forms. (Cresyl violet, × 250.) (AIP neg. 92264.)

* Personal communication to the authors.

tration of DDT. In 3 cats the spinal cord was sectioned at levels between the seventh thoracic and second lumbar segments. Eight to 20 days later each received by stomach tube 300 mg./kg. of DDT in peanut oil. Within 3 to 6 hours tremors developed in the muscles innervated above the transections, and potentials taken from these muscles showed a significant increase in action currents. The muscles below the transections failed to exhibit tremor, however, and no action potentials could be recorded from them. In 3 additional cats in which neurologic symptoms followed the administration of 300 mg./kg. of DDT, the brain stem was transected at the lower level of the mid-brain; 10 to 20 minutes later the symptoms reappeared. The conclusion drawn was that in *acute* experiments on the cat DDT exerts its effect on the portion of the central nervous system below the mid-brain and above the spinal cord, and that it apparently does not act on the spinal cord, the myoneural junctions, or the muscles.

Further evidence that the cerebellum may be the essential site of action of DDT has been gained from the electroencephalographic studies of Crescitelli and Gilman[3] on cats and monkeys. In animals in which tremor induced by DDT was abolished by curare and in which a central depressant, such as sodium pentobarbital, then was given, the subsequent administration of DDT intravenously led to electroencephalographic changes in both the cerebral cortex and cerebellum. The main effect on the motor cortex consisted of a change from the normal pattern of irregular bursts of waves at a frequency of 8 to 12 cycles per second to one of persistent rhythm with almost continuous and regular discharges at the same frequency, whereas a progressive increase in the amplitude of activity took place in the cerebellum, attaining within 1 to 2 hours after the injection of DDT a constant peak voltage with slight increase in the wave frequency. The tentative conclusion reached was that DDT acts primarily on the cerebellum, and that as a result the discharges are transmitted *via* efferent paths to the cerebral cortex, modifying its activity. When the use of a central depressant was avoidded and the curarized animal anesthetized lightly with ether, periodic electrical disturbances of a convulsive character occurred simultaneously in the cerebral cortex and cerebellum, and continued for a number of hours. The disturbances were always heralded by fast spike-like waves which were localized to the premotor cortex of the cerebrum on the one hand, and from the pyramis vermis and lobulus simplex of the cerebellum on the other. These spike-like waves occurred synchronously from the 2 structures, but with opposite polarity, *i. e.*, they were of positive polarity in the cerebral tracings, and of negative polarity in the cerebellar tracings. For the present, these findings are still open to some difference of interpretation as to the primary source of the waves. The possibility that the cerebral and cerebellar responses to DDT may be due to the discharge of afferent impulses by way of the spinal cord appears to be excluded by the finding that the electroencephalographic changes produced by DDT were not altered when the spinal cord was sectioned at the atlantoöccipital level.

The presence of slight to moderate liver damage in most of the animals is in accord with the findings of Bing, McNamara and Hopkins[1] that liver function is but little impaired, except terminally, even when relatively large amounts of DDT are administered. The sparing of the kidneys also concurs with their studies on kidney function.

Conclusions. From clinical observations as well as physiologic and electroencephalographic data, it appears that the cerebellum is the chief portion of the nervous system on which DDT acts. The same would seem to hold pathologically, inasmuch as degenerative changes in DDT-intoxicated dogs were restricted to the cerebellum, especially the dentate and roof nuclei. The degenerative changes in the

cerebellum were regarded as slowly progressive, since they were found only when relatively large doses were given over prolonged periods of time.

The systemic symptoms which occurred in some of the animals were not open to pathologic interpretation, since nothing of significance aside from slight to moderate degenerative change in the liver was observed.

We are indebted to Lt. Charles Boyers, CWS, for technical assistance, to Mrs. Helenor Wilder for examination of the eyes of 3 of the animals, and to Mr. M. A. Geisler for statistical analysis of the data.

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LATE NEURONITIS FOLLOWING PROVED AND SUSPECTED CUTANEOUS, FAUCIAL AND WOUND DIPHTHERIA

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The purpose of this report is to describe the clinical course of 20 cases† of late polyneuronitis following proved or suspected cutaneous and pharyngeal diphtheria. This syndrome is to be differentiated from the early diphtheritic neuritis occurring during, and within the first month after, the disease.

As evidenced by certain personal communications from Liebow,[12] Livingood,[13] and others, and by publications of Norris *et al.*,[16] Williams,[24] and the War Department,[23] as well as the histories of our own overseas patients, there has been considerable diphtheria in the Southwest Pacific theater of military operations in 1942, 1943 and 1944 and most probably more in western Europe and the Continental United States than in previous years. It has been suggested that the infection may have existed in the Pacific theater in the native population or been introduced by the Japanese invaders of the Solomon Islands, the North New Guinea area, Saipan and the Philippine Islands. Both Schick negative and Schick positive men acquired the infections and the Schick test in the milder cases occasionally remained positive after cure. The disease may occur as ulcerative skin lesions, typical or subclinical faucial infection, or both skin and pharyngeal involvement. Either the skin or pharynx may be the primary source of infection which then may spread to other regions.

The occurrence of cases of typical Guillain-Barré syndrome following cutaneous diphtheria was noted in 1918 by Walshe[22] during the first World War. Although Wilson,[25] Grinker,[8] Ederle[6] and others recognized the frequency of secondary postdiphtheritic polyneuritis, there has been a paucity of reports indicating the frequency of association of this syndrome following diphtheria until statements of recent military clinical experiences. The War Department *Bulletin*[23] comments on the occurrence of peripheral neuritis in a fifth of all diphtheritic dermatitis cases.

It is stated that the neuritis occurs from 2 to 4 months after the onset of the infection and of the early cranial nerve palsies. It is associated with elevated spinal fluid protein and generally is characterized by lost reflexes, motor weakness, paresthesias and hypesthesias of the extremities, especially the lower legs and feet. Certain reports fail to separate these cases from the ordinary early diphtheritic peripheral neuritis which occurs within the 1st month after infection. Whereas no fatalities have been reported, exclusive of 1 case, probably an example of early diphtheritic neuritis, as reported by Norris *et al.*,[16] many cases observed at Baxter General Hospital and in other continental and overseas hospitals have been very severe and have resulted, although infrequently, in significant motor or sensory residual disturbances. Some of these patients are so completely incapacitated at the height of their illness that they cannot lift their heads off the pillow or feed themselves.

The characteristic clinical picture of Guillain-Barré syndrome or infectious polyneuritis, or polyneuronitis, resembles these postdiphtheritic states. The Guillain-Barré syndrome may be summarized

* The author is indebted to Capt. H. L. Rudolph, M.C., Chief of Physical Therapy Section, for the study of electrical reaction and function of muscles, and to Lt. Col. M. H. Stiles, M.C., Lt. Col. C. H. Manlove, M.C., and Capt. W. Wolf, M.C., for their assistance in the study of patients.

† An additional case of neuronitis following prolonged faucial diphtheria has not been studied for a long enough period to warrant inclusion in the series.

as follows: the onset generally follows 5 days to 6 weeks after an upper respiratory or other infection; the initial symptoms are largely sensory, including pain in the extremities. This is followed closely by a progressive, bilateral symmetrical quadriplegia (predominantly proximal) which overshadows the sensory signs. Cranial nerves are generally involved, often the seventh nerve. The cerebrospinal fluid typically shows a high protein content without increased number of cells. The mortality is reported from 14 to 42%. The convalescence is slow but usually complete—moving rapidly once started, and the duration generally varies from 14 to 120 days. Drug therapy, including thiamine chloride, is currently ineffective.

Although there has been considerable disagreement in the application of the terms neuronitis and neuritis to this syndrome, the term neuronitis is herein used since it implies involvement of the nerve cells, axones and dendrites of the brain, spinal cord, spinal, cranial and autonomic ganglia and cranial and peripheral nerves. From pathologic studies on autopsy cases of Guillain-Barré syndrome (Roseman and Aring,[18] Lowenberg and Foster,[14] and others[3,4,8,9]) this widespread involvement has been demonstrated.

These pathologic findings may be briefly summarized as: 1. Shrinkage, vacuolization and destruction of nerve cells throughout the brain, spinal cord and ganglia, rarely extensive and occasionally associated with perivascular hemorrhage.

2. Axonal degeneration in the brain, spinal cord, especially the posterior columns, and cranial and peripheral nerves as evidenced by (*a*) swelling, corkscrewing, beading and fragmentation of the axis cylinders; (*b*) swelling and fragmentation of the myelin sheaths; (*c*) proliferation of the Schwann cells; and (*d*) occasional phagocyte and lymphocyte invasions—chiefly present in the peripheral nerves.

3. The spinal cord involvement was greatest in the cervical and upper thoracic and then in the lower lumbar regions. The involvement was heavy in the vagus nuclei and the peripheral nerves.

In addition to nervous system lesions, visceral pathologic changes have been reported, namely: 1. Fatty infiltration, mononuclear and polymorphonuclear cellular accumulations and focal degeneration of the liver.

2. Adrenal cortical cell degeneration.

3. Interstitial cellular infiltration of the kidneys without nephron damage.

4. Necrosis of muscle fibers and mononuclear and polymorphonuclear cellular infiltration of the heart. McIntyre[15] recorded electrocardiographic changes in a patient with Guillain-Barré syndrome, similar to those found in diphtheria, namely A–V conduction delay and S–T and T wave abnormalities.

An outline of the 20 cases is presented in Table 1. The patients varied in age from 20 to 35 years and there was only 1 female, Case 16, in the group. Three acquired pharyngeal diphtheria in the European theater of operations; 1 pharyngeal case was contracted in Spokane; 1 empyema with suspected diphtheria in Alaska; and the remaining 15 acquired pharyngeal or cutaneous diphtheria infections in the Southwest Pacific theater of operations. There were 62 cases of healed or active cutaneous diphtheria admitted into the hospital during the period from December 1 to February 15, of which 11 developed polyneuronitis. All of these 11 cases are included in the series of the 20 cases outlined in Table 1. Ten neuronitis cases accompanied or followed clinical cutaneous diphtheria showing characteristic anesthetic, punched-out lesions and partially to completely anesthetic, sharply defined scars.

One patient had exfoliative dermatitis with irregular areas of local infection. Two patients had both clinical diphtheria and pharyngeal diphtheria. Five patients had clinical pharyngeal diphtheria, although virulent C. diptheriæ could not be cultured from 1 patient. Two patients had neuronitis accompanying resistant empyema with avirulent diphtheroids in

TABLE 1.—SUMMARY OF 20 CASES

Case No. Initials Age Theatre Severity	Clinical: Skin ulcers	Clinical: Phar. diph.	Initial symptoms	Cranial nerves involved	Maximum involvement: Clinical	Maximum involvement: Electr. react. degen.	Maximum involvement: Reflexes
1. L.D.R. 35 Biak ++++	+	0	Numb hands and feet	V, VII	3C-2T, 2L-3S; 60d-bed, arms, legs, trunk	Ptl ++	Abs. Bi, Tri AJ, KJ
2. A.G. 24 New Guinea ++++	+	+	Tingling, numb hands and feet, slapping gait	(Early III, IX, X, XI); III, V, VI, VII	3C-2T, 2L-3S; 48d-bed, arms, trunk, legs	Ptl ++	Abs. Bi, Tri, AJ, KJ
3. J.F.S. 25 New Guinea ++	+	0	Can't lift R. arm, numb and tingling hands and feet; ache in arms legs	0	3C-1T, 3L-1S; can't comb hair, climb stairs; numb feet +	Ptl + R. shoulder, L. peron.	Abs. Bi, Tri, AJ, KJ
4. C.F.B. 29 New Guinea ++++	Exfol. Derm.	0	Numb and tingling feet, stumbling gait	0	L. 5L-1S, R. 3L-1S; bed, arms and legs	Ptl +	Abs. Bi, Tri, AJ, KJ
5. C.A.S. 35 New Guinea +	+	0	Numb fingertips	V?	Fingertips and 3L-2S; R. and L. toe-drop, weak arms; hypesthesia, hands and feet	0	Abs. Bi, Tri, AJ, KJ
6. H.A.O. 24 New Guinea +++	+	0	Tingling and numb fingertips, toes and soles	0	4C-3T, 3L-1S; bed-trunk, arms, legs involved	Ptl +++ Trunk, arms and legs	Abs. KJ, AJ, Bi, Tri
7. J.McC. 27 Alaska ++++	0	0 ? wound +	Numb face, arms and lower legs	V, VI, VII, VIII, X, XI, XII	5C-1T, 10T-1S; bed-ridden	Ptl gen. Arms, legs, trunk and shoulders	Abs. Bi, Tri, KJ, AJ, Abd and Crem
8. R.H.W. 20 Leyte +	+	+	Numb feet	0	7C-8T, 3L-1S; can't type or climb stairs	Ptl + Arms, legs	KJ ±, AJ Abs.
9. K.A.N. 25 Leyte +	+	0	Numb and tingling fingertips, R. ankle, L. toes	0	4C-3T, 3L-1S; toe-drop; can't climb	Ptl ± to ++ gen.	KJ ±, Bi, Tri, AJ Abs.
10. D.H.F. 29 New Guinea, Leyte +	+	0	Numb feet	III (accom.)	4L-1S; toe-drop, can't climb	0	KJ ±, AJ Abs
11. F.N.B. 29 Italy +	0	+	Numb fingers and toes	(X early) 0	Weak grip L. and climbing	0	AJ Abs.
12. H.H.S. 23 Leyte +	+	0	L. toe-drop, numb L. foot and ankle	0	Fell on walking, can't climb or hold arms up; toe-drop	Ptl + L. leg	KJ, AJ, Abd Abs.
13. H.G.H. 27 Leyte ++	+	0	Weak legs with climbing	0	7C-8T, 4L-1S; numb (stumbled), can't climb, weak grip	0	Normal
14. J.W. 33 Leyte ±	+	0	Weakness and aching of lower legs	0	Numb fingers and R. foot; loss vibr. sense R. foot; sl. weak legs	0 0	Normal Normal
15. V.T.R. 23 Belgium ++	0	+	Numbness, tingling of feet and fingers	(III, V, X, early) 0	Weak legs, slapping gait, can't hold fork or pen and L. shoulder weak	Ptl ++ Arms, legs	L. Bi, Tri Abs., L. KJ ±, AJ Abs.
16. L.H. 28 Spokane ++	0	+	Numb fingers and stumbling gait	(III, V, early) 0	Numb lower arms, hands, low legs, feet; can't walk or button clothes	Ptl Arms, legs	Abs. Bi, Tri, KJ, AJ and L. Abd
17. K.K.R. 25 Luzon ++++	0	+? empyema	Numb tingling of hands and feet; weakelevating of R. arm	(III, V, X, early) V	Bedridden, couldn't feed self, urine retention; hypesthesia 3L-1S	Ptl Hands, arms legs	Abs. Bi, Tri, AJ, L. KJ, R. KJ‡
18. J.A.C. 20 Germany +	0	+?	Numb feet and legs	(III, V, X, early) 0	Numb lower legs, feet and hands; can't climb stairs or descend; slapping gait	0	Abs. AJ
19. M.L.A. 29 ?Local infect. New Guinea Lichen planus	+	0	Numb tingling of fingers	0	Numb fingers and toes; weak grip, can't climb stairs	0	Abs. AJ, L. KJ, R. KJ ±
20. H.J.O. 30 Biak ±	0	+	Numbness of toes on walking	0	Tingling and numb feet and ankles; vibr. sense 0 L. metatarsals and toes	0	Abs. AJ

NOTE.—Under *Clinical-Phar. diph.*, and under *Cult. diph.*, +? indicates avirulent or doubtfully virulent diphtheria cultured. Under *Cranial nerves involved*, "early" indicates nerve involved at onset of diphtheria but recovered prior to late neuronitis. Under *Maximum involvement—Clinical*, numerals and letters indicate the cord segment involved, that is, 3C-2T signifies involvement from 3rd cervical to 2nd thoracic. Under *Maximum involvement—Electr. react. degen.*, Ptl signifies partial. Under *Maximum involvement—Reflexes*, Bi, Tri, AJ, KJ, signify biceps, triceps, Achilles

OF DIPHTHERITIC POLYNEURONITIS

Case No.	Residual signs and symptoms	Treatment	Dur. diph. (days)	Interval bet. diph. and neuronitis (days)	Recovery rate	Neuronitis duration (days)	Cult. diph.		Schick test	ECG changes	Spinal fluid	
							Skin.	Phar.			Max. tot. prot. (mg. %)	Coll. gold
1.	Numb fingertips, sl. weak on stairs; vibr. ± R. and L. L_1-S_1 and R. C_7-T_4; reflex changes: AJ ± and Bi, Tri ±	Penc. im.	104	70	+++	150	0	+	−	+	60	+++ Paretic
2.	Numb hands and feet, slapping gait; reflex changes: Bi, Tri, KJ, AJ +; rad and ul 0	Penc. im. Diph. antx.	45	30	+	85+	+	+	−	0	−	−
3.	None	Penc. local	(330±) 70	75	±	60	Healed	−	−	0	35	0
4.	Sl. weakness R. foot, peroneals and R. hand; hypesthesia of fingers; vibr. sense ± to 0 toes; reflex changes, none	Penc. im.	(180) 80?	30?	+++	140	Healed	−	−	+	79	+++ Paretic
5.	Sl. + fatigue of legs; reflex changes, none	Local	75	45?	+	125	Healed	−	−	0	25	+
6.	Vibr. sense ± R. hand and foot; sl. weak R. hamstrings; reflex changes: Bi, Tri, KJ, AJ ±	Penc. im. and local	(79) 58?	43	+++	78	0	0	−	0	80	++ Paretic
7.	Vibr. sense ± L. foot and knee, R. lower leg; weak L. peroneals; reflex changes: AJ R. ±; L. 0, KJ L. ±	Diph. antx. Penc. im.	(200) 90?	135?	+++	150	0	0	−	+	134	+ Paretic
8.	Vibr. sense ± in toes; reflex changes: AJ R. ±	Penc. im. and local	(190) 74?	56	±	110	+	+	−	0	25	0
9.	R. ser. ant. and delt. paralysis and atrophy; vibr. sense ± toes; reflex changes: L. KJ and AJ ±	Penc. im. and local	82	77	±	70	Healed	0	−	0	111	0
10.	Vibr. sense + feet and R. hand; weak hamstring; reflex changes, none	Penc. im. and local diph. antx.	78	47	+	87	+	+?	−	0	29	0
11.	Vibr. sense ± 2nd to 5th toes; reflex changes, none	Diph. antx.	34	45	±	104	−	+	−	+	21	0
12.	Sl. weakness abd., arms and vibr. sense 0 to ± lower legs and feet and 3L-4S vert.; reflex changes, none	Penc. im. and local	72	67	++	110	0	0	+	0	120	+ Tabetic
13.	Numb in region of ulcers on ankles; vibr. sense 0 to ± toes; reflex changes: R. KJ and AJ sl. reduced	None	40–98	32	±	103	0	0	−	0	60	0
14.	Vibr. sense ± to 0 in all toes and metatarsals; reflexes normal	Penc. local	90	60	±	95	0	0	+	0	42	0
15.	Sl. hyperesthesia, sl. weak R. arm; reflexes normal	Penc. im. diph. anth.	46	68	+	92	0	+	−	0	105	0
16.	Vibr. sense ± toes; reflex changes, none	Diph. antx.	7	30	+	124	0	+	−	0	40	0
17.	Vibr. sense ± toes and metatarsals; reflex changes: AJ 0	Penc. im.	130?	49	+ early +++ late	126	0	+?	−	+ (persists)	13	0
18.	Sl. hypesthesia to pin prick R. toes and 1st toe L. 0 to ±; vibr. sense R. all toes and metatarsals; reflex changes, none	Penc. im.	28?	58	++	48	0	+?	+	0	49	0
19.	Vibr. sense + to ± all toes and fingers; reflex changes: AJ 0, KJ R. ± and L. 0	Penc. im.	50	52	++	68	+?	0	−	0	20	0
20.	Legs buckled walking; loss of fine movement and dim sensation R. hand; vibr. sense ± to 0 toes and metatarsals	Diph. antx.	4	72	+	17	0	+	(+ℭ Diph.) −	0	63	0

or ...dle jerk, knee jerk, respectively. Under *Treatment*, Penc. im. or Diph. antx. indicates penicillin or diphtheria ant...xin administered by intramuscular injection. Under *Dur. diph. (days)*, and *Interval bet. diph. and neuronitis (da...)*, figures in parenthesis indicate undeterminable estimates of periods; figures followed by ? indicate known periods wit... 1 week.

the wounds, 1 responding to diphtheria antitoxin and the other succeeding bacteriologically unproved clinical diphtheria with faucial membrane formation showing an avirulent organism on culture.

The validity of the diagnosis of diphtheria in many of these cases could be doubted except for the currently well recognized clinical picture of cutaneous diphtheria. In only 3 instances was virulent C. diphtheriæ recovered from the skin lesions, but as has been previously stated most of these patients' lesions were clinically healed or nearly healed on arrival in the United States. In the instance of Case 17 the patient probably acquired a diphtheritic lesion of the skin of his right ear by contact in the ward of this hospital, but the diphtheroid organism obtained on culture proved avirulent. Because the lesions were healed no cultures were made on 5 patients. In all others pharyngeal and, where indicated, cutaneous or wound cultures were made. In only 1 patient (Case 10), who had pure cutaneous diphtheria, was a positive pharyngeal culture obtained, and this organism had a doubtful virulence.

Diphtheria antitoxin was found necessary in only 1 case of cutaneous diphtheria, Case 17, but it had been used overseas in 2 others, 1 of which, Case 2, was of extreme severity. It had been used in 4 of the 7 proved or suspected cases of pharyngeal diphtheria. The additional patient, mentioned previously in a footnote, developed severe late neuronitis in spite of receiving 120,000 units in treatment of a prolonged faucial diphtheria. The series is too small to comment statistically on the efficacy of diphtheria antitoxin in preventing the sequel of polyneuronitis but these histories indicate that such treatment will not uniformly prevent this sequel.

The clinical course of 20 cases of polyneuronitis in this series follows the pattern of the Guillain-Barré syndrome with certain exceptions. There was an interval of 30 to 75 days, excluding Case 7, between the onset of the skin ulcers and the neuronitis. In many instances the ulcers were clinically cured, although in only 2 instances were they completely healed at the onset of neurologic signs or symptoms. The onset of the polyneuronitis in 17 cases was evidenced by paresthesias and numbness of the hands and (or) feet followed, in a few days to 2 weeks, by motor signs consisting chiefly of foot drop and (or) weakness in lifting the arms. In 3 cases a stumbling gait or weakness in climbing stairs were the presenting symptoms. In contrast to the Guillain-Barré cases no patient complained of any significant pain. The advance of the process was generally slow for several weeks and then the motor symptoms abruptly increased.

Contrary to the usual involvement of cranial nerves, especially the seventh nerve, in the Guillain-Barré syndrome, only 5 of these cases showed transient cranial nerve involvement and only 3 had mild facial nerve involvement. The first and second sensory divisions of the fifth cranial nerve were involved in all 5 cases. In 2 of the 7 cases with faucial diphtheria, transient cranial nerve signs had been present during the acute phase. Four additional cases of early cranial nerve involvement failed to develop any signs of cranial nerve disease during the late form of neuronitis.

An unusually mild and prolonged course of the proved or suspected diphtheritic infection was characteristic for most of these patients who later developed polyneuronitis. The duration of the infection was estimated from 45 to 104 days with the majority persisting about 75 days. Of the cases of pure pharyngeal diphtheria, 3 showed prolonged courses of active infection, namely 32, 46 and 28 days, repeated administration of antitoxin being necessary in Cases 11 and 15. Cases 16 and 20 had normally short courses, with prompt response to antitoxin. Liebow[4] and Dudley[5] suggest that such mild diphtheritic infections fail to raise the concentration of antitoxin in the blood to a level which would prevent prolonged absorption of toxin or reverse the Schick

reaction in some cases. Only Cases 12, 14 and 18 of our series demonstrated a positive Schick reaction in the late stages of the disease. Case 18 was a patient with clinically characteristic pharyngeal diphtheria from whom it was impossible to culture virulent diphtheria bacilli. He received penicillin but no antitoxin. Cases 12 and 14 were cutaneous diphtheria. It has also been suggested that certain of these strains of diphtheria may differ from others more commonly encountered in the United States, in their tendency to produce mild prolonged infections.

The severity of the cases is indicated by symbols of ±+, ++, +++, ++++, indicating mild, moderate, severe and very severe attacks. Cases 14 and 20, classified as ±, had definite but minimal symptoms of paresthesia and weakness (of legs only in Case 20), had no loss of reflexes but loss of vibratory sense in the toes. Such cases might be readily missed unless the observer was alert to the characteristic signs and symptoms of the disease. Cases 1, 2, 4, 6, 7 and 17, classified as ++++, were all bedridden and required assistance in feeding and turning their bodies. No patient had interference with respiration, nor were cerebellar signs or mental abnormalities observed. Almost all cases demonstrated widespread loss of the deep tendon reflexes of the arms and legs and frequently of the abdominal and cremasteric reflexes. Cases 14 and 20, although otherwise characteristic, at no time demonstrated any loss of reflexes. A partial electrical reaction of degeneration of certain muscles was temporarily demonstrated in all grade ++ to ++++ cases and persisted in the right deltoid and serratus anterior in Case 9.

The recovery was often abrupt, which is less frequently observed in reports of the Guillain-Barré syndrome in which occasional cases are reported as persisting for 3 years. Recovery is generally complete with rare residuals of weakness, atrophy or sensory damage. The rate of recovery is indicated in Table 1 by 4 symbols from ±, a slow recovery rate, to +++, indicating return of function from a completely bedridden helpless patient to an active ambulatory state within 3 weeks.

The criteria for complete recovery are difficult to define. When function and sensation returned to a constant state for 1 to 2 months the patients were adjudged as recovered. The duration of the disease varied from approximately 50 to 155 days with the exception of Case 20, the mildest of the series, which lasted 17 days. There were only 5 patients who had exhibited a complete areflexia and then recovered normal reflexes after 3 to 7 months observation, namely Cases 3, 5, 11 and 15 within 4 months and Case 1 only after 7 months. Cases 14 and 20 at no time showed loss of reflexes. Case 2 was not followed after the 3rd month being transferred to another hospital while still exhibiting considerable involvement but in a recovery phase. Nine patients demonstrated slight muscular weakness chiefly in the peroneal, hamstring and hand muscles. Only in Case 9 was persistent weakness and atrophy of marked degree noted after apparent recovery, and this was in the right serratus anterior and deltoid muscles (Figs. 1 and 2). Subjective paresthesia and numbness were persistent in only 2 cases, excluding Case 2, but slight hypesthesia to pain and touch in fingers and toes was present in 4 cases. The most constant residual finding, exclusive of hypesthesia in or adjacent to the diphtheritic skin ulcer scars, was a reduced perception of tuning fork vibration in the fingers and toes. In contrast to the early stages, in the late recovery phase the pattern of sensory diminution did not follow segmental or characteristic major peripheral nerve distribution. "Glove" or "stocking" type anesthesia was common and suggested distal involvement of peripheral nerves. The irregular involvement of different phalanges excluded hysterical origin. Occasionally there was vibratory hypesthesia of the spinous processes of the lumbar and sacral vertebræ, in the long bones of the extremities and the ilia.

Frequently hypesthesia of the soles and

palms accompanied the recovery and persisted. This may have been partially due to the hyperhidrosis commonly observed in these patients.

fatality from respiratory paralysis or a complicating pneumonia could occur in this type of case.

The spinal fluid protein in Guillain-

FIG. 1.—Case 9. Anesthetic, pigmented scars of healed cutaneous diphtheria.

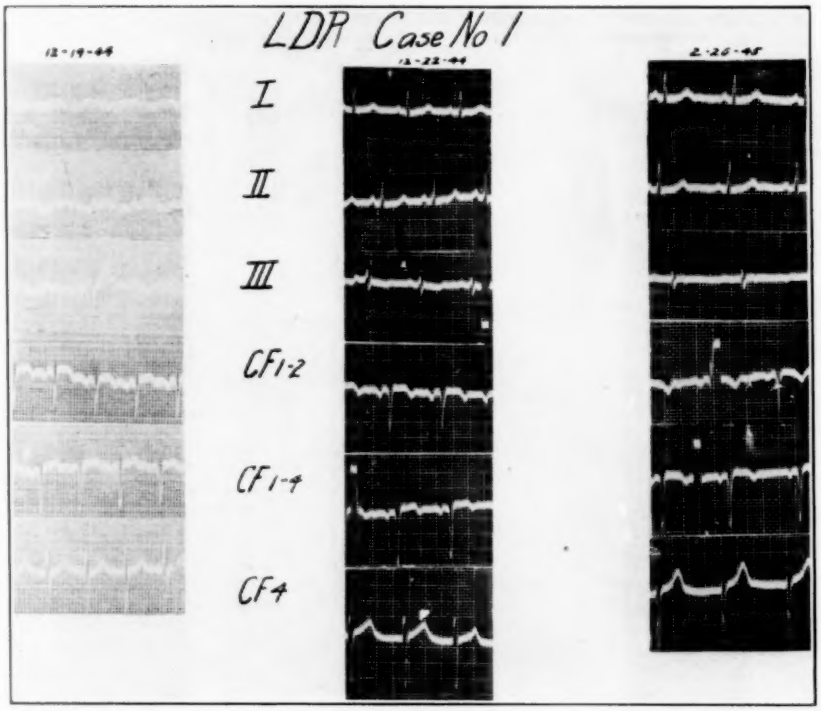
FIG. 2.—Case 9. Residual serratus anterior and deltoid muscle paralysis resulting in winging of right scapula.

In contrast to a mortality of 14 to 42% in certain reports of the Guillain-Barré syndrome, no fatalities have been reported from these postdiphtheritic cases, although the extreme paresis suggests that

Barré syndrome is characteristically elevated from 70 to 400 mg. per 100 ml., generally without an increase of cellular elements. In Liebow's[12] series the spinal fluid protein varied from normal to

125 mg. per 100 ml., with the majority varying from 60 to 80 mg. per 100 ml. Only 9 of our cases demonstrated spinal fluid total protein content of 60 mg. per 100 ml. or more, 2 of which were 120 and 134 mg. per 100 ml. Five of our series demonstrated a paretic (first zone) type of colloidal gold curve and 1 case a mid-

myocarditis found in these patients was not a result of diphtheria but a complication of the neuronitis syndrome. Myocarditis with electrocardiographic abnormalities has been reported in Guillain-Barré syndrome and late myocarditis was noted in 1 of Liebow's[12] cases and has been mentioned in other personal communica-



A B C

FIG. 3.—Electrocardiograms of Case 1. *A*, Records of Dec. 19, 1944, taken during advance of polyneuronitis. Depression of S–T segment in Lead I and Lead II with elevation in Lead CF_{1-2} (chest lead in 2nd right intercostal space). T wave depressed in Leads I and II and inverted in Lead III and upright in Lead CF_{1-4} (chest lead in 4th right intercostal space). *B*, Records of Dec 22, 1944, show marked improvement with no significant change in the clinical state. *C*, Records of Feb. 26, 1945, show further improvement in S–T segment and T wave changes in Leads I, II, III and CF_{1-2} and CF_{1-4}. Clinical recovery was well advanced at this time.

zone type. The total protein content, when elevated, increased in proportion to the severity of the symptoms. A convalescent elevation is not uncommonly observed in Guillain-Barré syndrome and was present in Case 20.

Although we have no early electrocardiograms except in Case 17, it is our belief that with the exception of this case the

tions. Tachycardia was present in 7 of our cases and also definite but transient electrocardiographic changes in 5 of this series (Figs. 3 and 4). In Case 17 electrocardiographic abnormalities persisted with little change from the onset of the acute diphtheria through complete recovery of the neuronitis.

No evidence of renal damage was noted.

Two instances of acute hepatitis (Cases 7 and 20) occurred during the height of the illness. These may have been coincidental attacks insofar as acute hepatitis was prevalent at the time in the area from which these patients were evacuated.

Drug therapy, including thiamine chloride, is reported as worthless and no change in the clinical course was made by daily

motor function in these patients. Case 6, who was completely bedridden and unable to lift his head or extremities for nearly 3 weeks, demonstrated no muscle atrophy and approximately normal use of his arms, legs and trunk within 10 days of the first time he was able to stand upright. This would be a remarkable recovery for any bedridden patient, but for such a

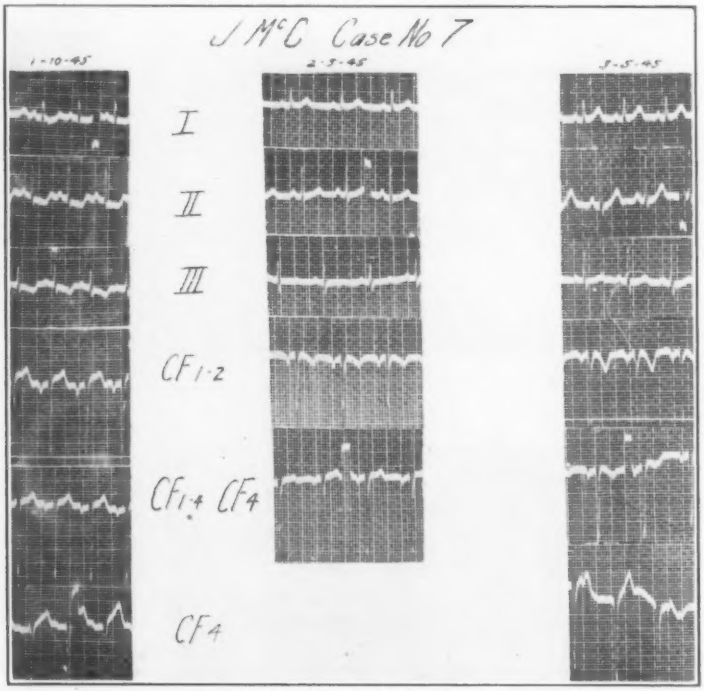


FIG. 4.—Electrocardiograms of Case 7. Records of Jan. 10, 1945, taken during advancing phase of polyneuronitis. Depression of S–T segment in Leads I, II and III with elevation in Leads CF_{1-2}, CF_{1-4} and CF_4. T wave depression in Leads I and II, inversion in Lead III and upright in CF_{1-2} and CF_{1-4}. Records of Feb. 5, 1945, taken during severe phase of the disease. S–T segments are isoelectric, T_1 and T_2 are upright, T_3 isoelectric and T CF_{1-2} inverted. Records of Mar. 5, 1945. Taken in early recovery phase, shows return to normal pattern with T_3 now upright.

doses for 2 to 4 weeks of 100 mg. thiamine chloride intramuscularly in 4 cases during the advancing phase of the process. It has been suggested that prostigmine may be valuable in the paralytic phase of this disease, but it was not used in this series of patients.

Physiotherapy in the form of daily massage and graded exercises results in prevention of atrophy and the loss of

patient with generalized paralysis it was a strong indorsement of this form of treatment.

The following is a more detailed review of 3 cases in the series, the first 2 being a mild and a severe attack following cutaneous diphtheria, the third being a severe one in which virulent diphtheria bacilli were suspected of being present in an empyema wound, but never demonstrated.

Case Histories. Case 6. H. A. O. (Fig. 5.) This 24 year old enlisted man developed a vesicular dermatitis, generalized, while in combat and living on C & K rations, in the Southwest Pacific theater of military operations in mid-November 1944. The dermatitis cleared with local treatment and he returned to duty in 2 weeks, but about Dec. 6 1944, about 15 ulcerated lesions appeared on both lower legs, ankles and feet. He was hospitalized with a mild fever (maximum of 100.4° F.) and was ulcers had started to heal. About Jan. 18, 1945, he noted numbness and tingling of all his finger tips and within 24 hours similar sensations in the toes and "balls of the feet." He was admitted to Baxter General Hospital on Jan. 23, 1945, with about 10 partially healed ulcers varying from 5 mm. to 4 cm. in diameter and with the above-mentioned symptoms of numbness and tingling in his hands and feet and a tendency of his legs to buckle under him when he walked. Gentian violet solution was applied to the ulcers

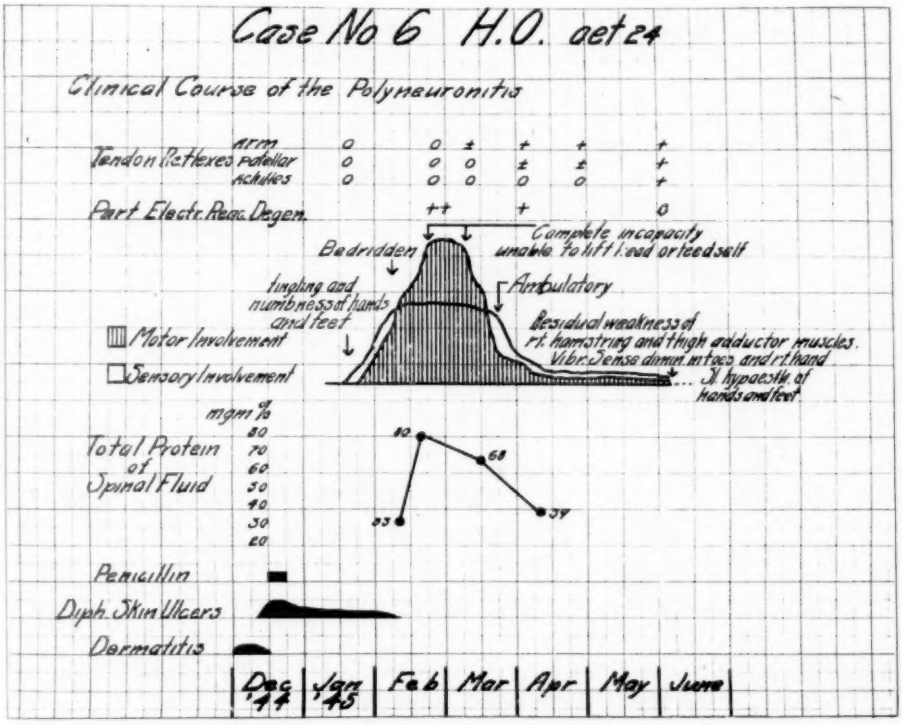


Fig. 5.—Case 6. Chronologic diagram of clinical course and spinal fluid protein changes.

treated with sulfadiazine orally, penicillin intravenously and local saline and penicillin moist dressings on the lesions. Although the skin lesions were characteristic diphtheritic ulcers, round or oval with sharply demarcated borders and grayish brown membranes which later crusted, *C. diphtheriæ* was not isolated by culture. No diphtheria antitoxin was administered.

He was evacuated to the continental United States in early January 1945 as a litter patient by which time many of the and dry dressings were used and the ulcers healed completely within the next 4 weeks, with smooth anesthetic surfaces and heavily pigmented areolæ.

A neurologic examination on Jan. 25, 1945, revealed hypesthesia, hypalgesia and diminished temperature sensation in both hands and lower legs, and weakness of the muscles of the shoulders, arms and legs, and especially the posterior deltoids, muscles of the hands and the hamstring and peroneal groups. There was reduced vibratory sense

of the bones of the hands, forearms, feet and lower legs. Biceps, triceps, patellar and Achilles tendon reflexes and the abdominal and cremasteric reflexes were absent bilaterally. There was no cranial nerve involvement. The leukocyte blood count was 11,600 per c.mm. (9% eosinophils). The spinal fluid on January 27 revealed 1 cell per c.mm., 33 mg. per 100 ml. total protein, a heavy trace of globulin and a colloidal gold reading of 2111110000. The Schick test was negative.

His condition remained stationary with the exception of a diminution of the numbness and tingling of the feet and hands between February 24 and March 14. Studies of sensory changes in this period illustrate a segmental distribution of hypesthesia, hypalgesia, diminished temperature sensation, vibratory sense and proprioception as in Figure 5, namely C_4 to T_4 and L_2 to S_1 on the right and C_4 to T_3 and L_4 to S_1 on the left. Asterognosis and atopognosis existed in the hands and feet. Muscle studies revealed

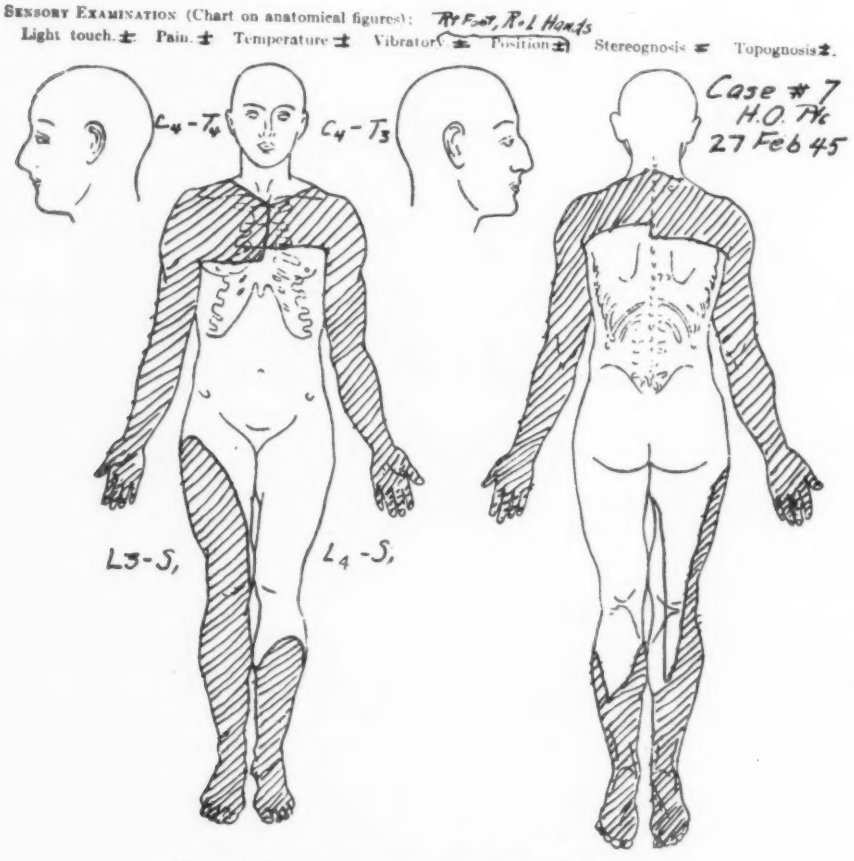

Sensory Examination (Chart on anatomical figures): Rt Foot, R & L Hands
Light touch ± Pain ± Temperature ± Vibratory ± Position ± Stereognosis ± Topognosis ±
C4 - T4
C4 - T3
L3 - S1
L4 - S1
Case # 7
H.O. Pfc
27 Feb 45

Fig. 6.—Case 7. Pattern of hypesthesia and hypalgesia

His sensory symptoms remained unchanged but the weakness slowly increased and by February 12 he was unable to stand unassisted or to lift his arms to comb his hair. By February 24 he was unable to elevate his trunk, head or legs, to turn himself in bed or to lift his forearms to feed himself. reduced power of all muscle groups of the trunk and extremities and a "poor" rating (inability to move against gravity) of the posterior deltoids, all hand muscles, hip rotators and gluteals, bilaterally, and of the left hamstring, peroneal groups and gastrocnemius and of the right middle and lower

trapezius muscles. Partial electrical reaction of degeneration was noted in these muscles, as evidenced by a sluggish reaction to strong faradic stimulation. Slight reaction of degeneration was noted in the other muscles of the upper and lower extremities.

The tendon reflexes were still absent on February 24, but the right epigastric and right cremasteric were present, although sluggish.

positive globulin, and a negative colloidal gold test.

On April 7 the tendon reflexes of the upper and lower extremities with the exception of the right Achilles tendon reflex which was absent, had returned although they were faint. There was demonstrable weakness of the right thigh adductors and hamstring groups and hypesthesia of the entire right foot and left second to fifth toes as well

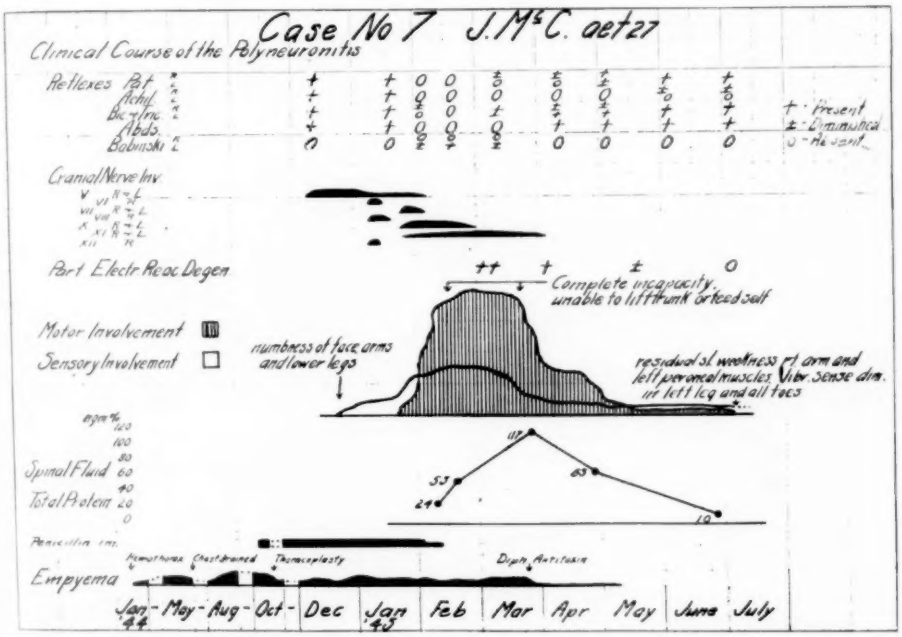

Case No 7 J.M.C. oct 27
Clinical Course of the Polyneuronitis
Reflexes
Cranial Nerve Inv.
Part Electr Reac Degen
Complete incapacity, unable to lift trunk or feed self
Motor Involvement
Sensory Involvement
numbness of face, arms and lower legs
residual slt weakness of arm and left peroneal muscles. Slt. sense dim. in left leg and all toes
Spinal Fluid
Total Protein
Empyema
Thoracoplasty
Jan 44 May Aug Oct Dec Jan 45 Feb Mar Apr May June July

FIG. 7.—Case 7. Chronologic diagram of clinical course and spinal fluid protein changes.

The spinal fluid on February 19 revealed no cells, 80 mg. per 100 ml. total protein, colloidal gold of 3211100000 and positive globulin test (Pandy).

Improvement in muscle power started abruptly about March 10 and by March 18 he could feed and care for himself in bed. He was able to stand unassisted and walk assisted by March 27 and by April 7 was actively ambulatory. Muscle tests on March 23 showed that all muscles rated good or normal in the lower extremities, but the hand muscles, particularly the interossei, were still poor to fair. Partial reactions of degeneration were still noted.

On March 15 the spinal fluid showed 3 cells, 68 mg. per 100 ml. of total protein, as reduced vibratory sense of the phalanges of the hands and feet and of the right metatarsal bones.

Improvement continued slowly with toe drop and slapping gait and slight general leg weakness until about May 1, but paresthesias had completely disappeared by April 22. On return from furlough on June 4 his spinal fluid showed 2 cells, 39 mg. per 100 ml. total protein, a negative colloidal gold test, and a trace of globulin. All tendon reflexes and superficial reflexes were present but the Achilles reflexes showed diminished force. There was slight hypesthesia of the toes of the right foot and in and adjacent to the scars of the ulcerative lesions, the dorsum of the left foot and toes

and anterior lower two-thirds of the left lower leg. Vibratory sense was diminished in all toes and in the right and left fourth and fifth metatarsal bones. There was no demonstrable muscle weakness and electrical reactions were uniformly normal.

Thiamin chloride in doses of 200 mg. per day was given intramuscularly without apparent effect in the advancing stages of the disease. Massage and passive and active exercise were used through the entire course in progressive degrees. The constant attention of the physiotherapist was probably responsible for the rapid return of strength and for complete absence of muscle atrophy after the process had started to recede.

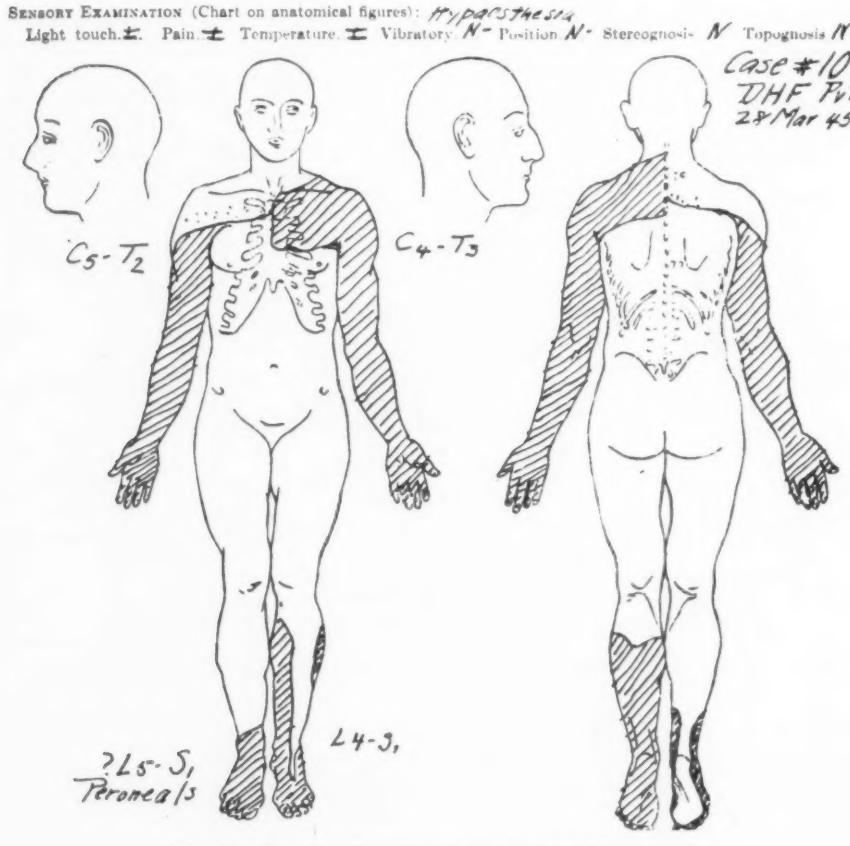


Fig. 8.—Case 10. Pattern of hypesthesia and hypalgesia.

Case 7. J. McC. (Figs. 6 and 7.) This patient, age 26, gave a history of onset of his present illness in January 1944 while stationed in Alaska, at which time he abruptly developed shortness of breath. This became increasingly severe in the next 24 hours until he was hospitalized at which time the presence of a massive spontaneous hemothorax on the left was determined by thoracentesis. No significant trauma preceded the hemothorax and no cause was found for it at later investigations. After a second tapping he developed fever and empyema was diagnosed. On April 19 he was transferred to Hammond General Hospital, California, and on May 24 a thoracotomy was done with resection of the eighth and ninth ribs on the left. Following this his wound was irrigated daily with Dakin's solution, and upon admission to this hospital the empyema cavity contained approximately 180 cc. of fluid. For approximately 1½ months before admission the size of the space had not altered appreciably.

His general condition upon admission to this hospital was good and he was ambulatory. Because the space was not obliterated by October 23, a Schedé thoracoplasty, with resection of the fourth to ninth ribs with complete unroofing of the space was carried out. The patient received penicillin postoperatively until November 12 at which time the space measured approximately 50 ml. The space continued to reduce in size for the succeeding 4 weeks. His general condition was satisfactory, but about November 24, the patient began to complain of pain in the left chest and a friction rub was noted. Examination of the wound was negative and there was no evidence of a bronchopleural fistula. In December the space contained about 10 ml. of fluid and there was considerable amount of granulation tissue about its opening. About this time the patient began to run a fever of 100° to 101° F. He complained of pain around the opening of the wound and the wound itself became inflamed with a shaggy dirty coating of fibrin upon it, and a tendency toward ulceration of the granulation tissue and skin about the opening of the wound. The patient continued to run a septic type of fever and have pain in his chest. On December 13, when increased drainage of the empyema was noted and the space reopened, it was found to hold approximately 50 ml. of fluid. It was now noted that a very definite cellulitis of the wound had developed and the infection was indolent, characterized by the production of considerable purulent material

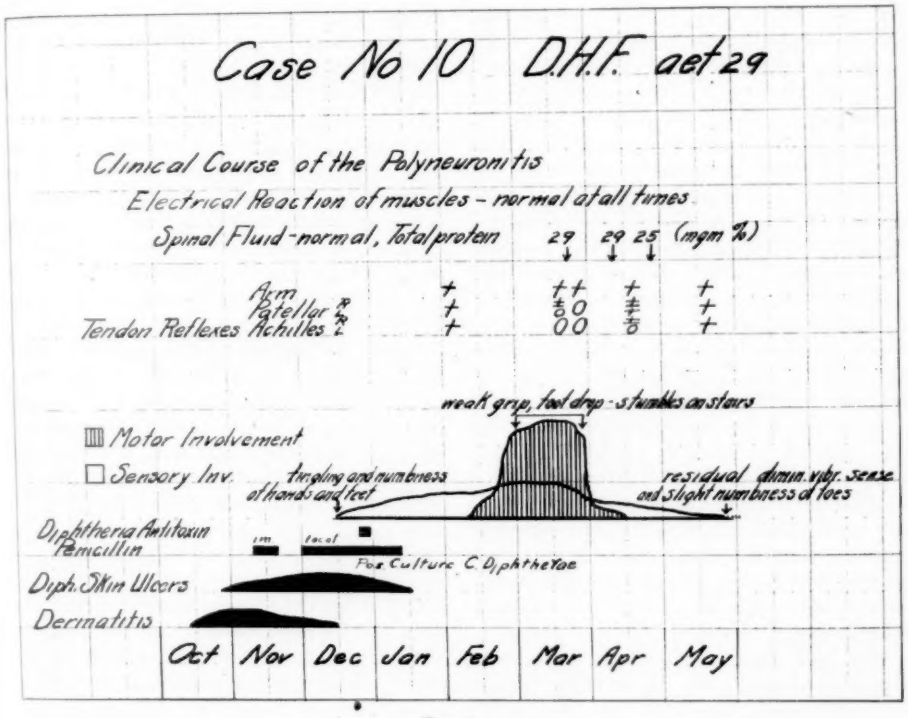


FIG. 9

shaggy fibrin coating on the pleural surfaces, and a tendency toward ulceration of the skin borders around the wound. Because of the chronicity of the infection, material from the wound was stained, cultured and injected into a guinea pig in search of tubercle bacilli but none were found. Because of the cellulitis of the wound Roentgen ray radiation was given and there was some moderate improvement of the external appearance of the wound. Penicillin was given both systemically and locally

without much alteration of the course of the disease.

About the end of December 1944, he rather abruptly developed numbness and paresthesias, and hypesthesia was demonstrated in the distribution of the fifth cranial nerve, and the ninth to eleventh thoracic nerve segments, especially on the right, the fifth to eighth cervical segments and the first thoracic segments on the right and left. These changes involved the lower neck and portions of the arm, the upper chest and a band around the mid-chest and upper abdomen. This area showed hypesthesia, hypalgesia and diminished temperature sensation. The symptoms and signs increased in severity and about Jan. 10, 1945, he developed diplopia on looking towards either side, due apparently to an involvement of the right and left sixth cranial nerves. This cleared in a period of about 1 week. On January 18 there was slight paralysis of the left twelfth cranial nerve noted by the tongue protruding to the left, and there was a slight persistent weakness of the right external oblique ocular muscle.

From January 1 to 20 he complained of tinnitus in his right ear with slight impairment of hearing on that side indicating involvement of the right eighth nerve. He had a moderate headache during January. The process advanced through the middle and end of January and by February 1 there was difficulty in swallowing indicating involvement of the motor roots of the fifth and possibly tenth cranial nerves. There was difficulty with phonation and bilateral hypesthesias of the face. Whereas the deep muscles and cutaneous reflexes had been normal on January 18, all tendon reflexes in the arms and legs including knee jerks and ankle jerks and all abdominal, cremasteric and corneal reflexes were found to be absent. He had an atypical Babinski reflex on the right. Weakness of the legs had developed most notably in the quadriceps, peroneals and the hamstring muscles, and there was hypesthesia and paresthesias from D–10 to S–2.

By February 21 the weakness had increased especially in the shoulders and arms, and there was some atrophy of the interossei muscles. His spinal fluid, which earlier was not abnormal, at this time showed a total protein of 53 mg. per 100 ml. About February 20 he developed an acute hepatitis as evidenced by jaundice, light stools, malaise and nausea with slight rise of temperature over his previous level.

The jaundice and laboratory evidences of hepatitis disappeared within 2 weeks but throughout the last week of February and all of March he was completely bedridden being unable to feed himself, lift his head or turn his body. Throughout the entire period he had demonstrated a moderate fever. His Schick test was negative and cultures deep from the chest wound showed avirulent diphtheroid organisms. In spite of this fact the use of diphtheria antitoxin was indicated in view of the nature of the wound and the neuronitis which had developed. On March 24, 20,000 units were administered and as a result of this his temperature returned to normal in 3 days and remained unelevated. There was a marked improvement shortly demonstrated in the character of the wound and rapidly diminishing discharge from the empyema cavity which spontaneously healed.

About April 1 he abruptly showed improvement in the neuronitis, although as early as the middle of March there was a return of sluggish knee jerks. The total protein of the spinal fluid was 117 mg. per ml. on April 5. By April 14 he showed general improvement in strength, and was able to stand and walk with only moderate assistance. Improvement continued rapidly and about May 20 he was aware of no significant weakness. However, the knee jerks were diminished as was the right ankle jerk and the left ankle jerk was absent. There was definite diminished vibratory sense in both feet and the right patella. His spinal fluid protein on June 8 still showed 60 mg. per 100 ml.

The electrocardiogram on January 10 showed depression of S–T intervals and flattening of T_1 with inversion of T_2 and T_3. The electrocardiograms of early February, March and April had returned to a normal pattern.

At the time of his discharge, July 4, 1945, he presented only slight weakness of the dorsiflexors of both feet and a slight consciousness of a slapping gait on the left due to foot drop when walking rapidly. His ankle jerks were very sluggish even with reinforcement but the knee jerks were present although the left was faint. He had no clean-cut Babinski reflex, although the right

plantar reflex occasionally showed an atypical dorsiflexion of the great toe. There was a loss quantitatively of vibratory sense of all the toes and in the metatarsal bones and the internal malleolus on the left. He had gained 35 pounds from his lowest weight, as of April 1, and his general condition was excellent. There was no evident muscle atrophy. His general muscular strength was excellent with the exceptions noted above.

Case 10. D. H. F. (Figs. 8 and 9.) This 29 year old infantryman developed a mild dermatitis of his lower legs in October 1944 when in the Southwest Pacific theater of operations. Ulcerative lesions appeared on both lower legs, ankles and feet and 1 on each wrist by November 1. They increased in number and size requiring hospitalization on December 1. Virulent C diphtheriæ was cultured from an ulcer and a diphtheroid organism of doubtful virulence from the throat on December 9. Penicillin was administered intramuscularly for 6 weeks beginning December 10 in amount of 120,000 units per day, and as an ointment on the skin lesions. On December 27, 40,000 units of diphtheria antitoxin were given intramuscularly. The skin lesions slowly healed and were smoothly epithelialized by Feb. 15, 1945.

About Dec. 15, 1945, slight numbness and tingling of the toes and numbness of the feet and ankles was first noted and about January 12 the numbness had extended up the left lower leg and there were paresthesias and numbness of both hands and wrists. This was not troublesome and the history was elicited only on specific questioning. He had moderate difficulty in focusing his eyes on reading from Dec. 15, 1944, to Feb. 1, 1945.

Physical examination on February 10 revealed slight hypesthesia to pain, touch and temperature from the fourth lumbar to the first sacral dermatomes and slight reduction of vibratory sense in the toes. There was slight weakness of both deltoid muscles. All superficial skin and deep tendon reflexes were normal and the spinal fluid was normal, namely 29 mg. per 100 ml. of total protein, 1 cell per c.mm. and a normal colloidal gold determination.

About February 15 he first noted weakness of the grip of his hands, a slapping gait with foot drop and difficulty in ascending or descending stairs. This weakness was observed while the patient was home on furlough and on his return to the hospital on March 25 improvement was evident. Examination on March 28 revealed an absent right patellar reflex and absent Achilles reflexes bilaterally with weakness of both quadriceps femoris, hamstring and peroneal groups and the extensor muscles and intrinsic muscles of the hands. There was hypesthesia of both hands and wrists and of the third lumbar to the first sacral segments bilaterally except for hyperesthesia of the right sole.

The patient's condition improved slowly. Repeated spinal fluid examinations were normal. By April 20, 1945, he complained only of slight numbness of the feet which were hypesthetic and slight weakness of the left leg. The patellar and left Achilles reflexes were present but faint and the right Achilles reflex was absent. At the time of his discharge on May 28, 1945, he had no complaints but there was slight weakness of the left hamstring muscles, vibratory sense lost in the right great toe and diminished vibratory sensation in the phalanges of the other toes and the right fingers and wrist bones. All tendon reflexes were normal at this time.

Summary and Conclusions. Twenty cases of late polyneuronitis are presented following proven or suspected cutaneous and faucial diphtheria. This syndrome differs from the early diphtheritic neuritis commonly observed. Approximately 20% of all cases of cutaneous diphtheria acquired in the South Pacific theater of operations, observed at the hospital in which these studies were made, developed polyneuronitis.

The clinical picture and spinal fluid findings closely resemble the Guillain-Barré syndrome with the exception that pain was not a symptom in any case.

The initial symptoms occurred generally from 1 to 3 months after the onset of the diphtheria. These symptoms were commonly numbness and paresthesias of the hands and feet. At the height of the illness, 5 of the patients were completely incapacitated, but several presented only minor sensory and motor disturbances

and the neurologic changes would have been overlooked without careful interrogation and physical examination.

Partial electrical reactions of degeneration of the involved muscles were obtained in all the severe cases.

The segmental character of motor and sensory involvement, generally C_1 to T_2 and L_3 to S_1 during the early and most severe stages of the disease, receded to signs of irregular distal peripheral neuritis. Recovery was generally abrupt and the commonest residual signs after 4 to 7 months observation were absent Achilles and patellar reflexes and diminished vibratory sense in the toes. Only 1 patient demonstrated marked residual loss of motor power, localized in the right serratus anterior and deltoid muscles.

Massage and passive and active exercises throughout the course of the disease apparently hastened the return to normal motor function and prevented muscle atrophy.

It is believed that the frequency of this syndrome following current diphtheria epidemics, both overseas and in the United States, as contrasted to its rarity in this country in recent years, may be attributed to prolonged courses of the diphtheria infections. It has been suggested that the infecting bacteria in this type of case have poor antigenic properties, and this concept is supported by the persistence of a positive Schick test in 2 of the patients.

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NEEDLE BIOPSY OF THE LIVER

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Needle biopsy of the liver has gained popularity slowly. The first recorded puncture was performed in 1833 by Stanley[2] to drain an abscess. Probably the first puncture for the purpose of biopsy was done by Lucatello[10] in 1895. Although used not infrequently in Europe, the procedure was for the most part neglected by American workers until the advent of widespread epidemic hepatitis in World War II.

From our experience with about 100 biopsies we believe that frequent use of this procedure is justified. The first 79 of these biopsies have been analyzed to estimate the chances of obtaining satisfactory material for microscopic examination as well as to determine the diagnostic value of such a procedure.

There are 2 general methods of doing needle biopsy of the liver. In 1 a very small bore needle is introduced into the liver with or without the administration of an anesthetic and a few cells are aspirated with a small syringe. These are expressed onto a slide, smeared and examined directly and again after staining, usually with a Romanovsky dye. Although this method is safe, its proponents[4,5,7,16,18] freely admit that the study of stroma and architecture is impossible with the specimen obtained. They do state, however, that frequent diagnoses are possible.

The other method employs a larger needle which yields specimens of tissue large enough for the preparation of paraffin sections. This was originated in 1923 by Bing[4] and Olivet, quoted by Olivet,[11] and extended by Olivet[11] in 1926. This method has been attended by a certain degree of risk. Olivet[11] reported 2 deaths from hemorrhage in 140 biopsies. In 1939 Inversen and Roholm[8,13] did 160 biopsies on 114 patients using the large needle technique through an intercostal approach in the posterior axillary line. Satisfactory specimens were obtained in 77.5% of the cases and 2 patients showed clinical signs of moderate to marked intraperitoneal hemorrhage. However, the patients died later and at autopsy it was thought that the deaths were not due to hemorrhage.

Baron,[1] who reported the first liver biopsies in the United States, used a technique similar to that of Iversen and Roholm except that the liver was approached from below the right costal margin anteriorly. In 49 biopsies on 36 patients he had 1 death from hemorrhage; in 1 of the patients he obtained a small piece of colonic mucosa without apparent ill-effect to the patient.

More recently, Tripoli and Fader[17] reported 14 cases done with the Silvermann[15] needle from the anterior subcostal approach without complication. Dible, McMichael and Sherlock[3] performed biopsy on 126 cases of acute hepatitis using the technique of Iversen and Roholm with 1 death due to intraperitoneal hemorrhage. Two other patients showed signs of intraperitoneal hemorrhage within 24 hours of the procedure but did not die. Subsequently, 2 other patients died, 1 having acute hepatic necrosis as shown at autopsy and the other having a large amount of blood-stained ascitic fluid.

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They concluded that "the technique cannot be recommended as a routine procedure." Kalk and his collaborators[9] reported biopsies obtained by combined laparoscopy and liver puncture with a 2 mm. cannula having a saw-toothed edge. There were no complications in 123 patients studied over a 2 year period.

Hoffbauer,[6] on a basis of experience gained in the performance of 65 biopsies, recommended the use of a modified Silvermann needle and found the procedure safe in the presence of a large and easily palpable liver but did not advocate it for the normal sized liver. More recently, however, 1 severe hemorrhage has been reported from his Clinic.[6a] Raby[12] added a case of fatal hemorrhage in his series to bring his collected total to 7.

and more recently the Roth-Turkel,[14] consistently good results have been obtained. The Roth-Turkel needle (Fig. 1) consists of an outer trocar with stylet and an inner hollow needle with small saw-teeth at the end. The trocar is advanced to the surface to be examined and the stylet removed. The inner needle is introduced and slowly advanced and rotated to cut out a core of tissue about 2 mm. in diameter. The end is moved slightly to free the core and the needle withdrawn as negative pressure is maintained with an attached 20 cc. syringe. A cylinder of tissue 0.2 cm. by 2 or 3 cm. is usually obtained.

The procedure is done at the bedside without preparation except for mild sedation for apprehensive patients. The liver is palpated and unless there is a definite nodule to be entered, a spot a few centimeters to the right of the xiphoid process and below the costal margin is selected. The skin is cleansed and prepared with alcohol and iodine. A sterile drape and gloves are used. The skin is infiltrated with 1 or 2% procaine and the infiltration is carried down to and including Glisson's capsule if possible. The skin is incised with a bistoury and the biopsy accomplished, the needle usually being directed upward and to the right toward the center of the liver. The activities of the patient are not limited as a result of the procedure.

There are certain risks which the procedure entails. Possible hazards include excessive bleeding into the peritoneal cavity or abdominal wall, perforation of the large or small intestine or gall bladder, introduction of infection or spread of localized infection into the general peritoneal cavity, and injury to nearby viscera such as the kidney, adrenal gland, or pancreas.

TABLE 1.—TOTAL NUMBER OF BIOPSIES DONE EACH YEAR WITH THE PERCENTAGE OF SUCCESSFUL ONES (4 of the 5 in 1943 After July 1)

Years:	1939–40	1941	1942	1943	1944	1945	Total
Biopsies	11	6	8	5	11	38	79
Successful	6	3	6	5	10	34	68
% successful	54.5	50.0	75.0	100	90.8	89.5	86.1
Autopsied	3	2	3	0	3	7	18

In the Cleveland City Hospital from the latter part of 1939 to July 15, 1945, 88 needle biopsies of the liver were done on 79 patients. Nine of these were done postmortem, 4 antemortem with peritoneoscopy control and 67 antemortem without peritoneoscopy. The procedure was done by several different physicians and the pathologic material was studied by different pathologists. For more accurate evaluation the study has been divided into 2 periods. The first part, extending from 1939 to July 1, 1943, includes 26 biopsies which were done without special instruments and with only a moderate degree of success—61.5% (Table 1). The technique during this time consisted of introduction of a large bore needle into the liver and aspiration with a syringe. Specimens consisted of powdery flecks of tissue which were fixed in Schaudinn's solution centrifuged, and sectioned. During the second period from July 1, 1943, to July 15, 1945, by use of the Silvermann[15] needle

In our series there were no serious consequences. Nine patients complained of abdominal pain for varying periods after the procedure, the usual period being for 1 or 2 days, but 2 patients continued to complain for 5 days. One patient had moderate epistaxis following the procedure. In 1 case peritoneoscopy was done the day following the biopsy, and except for a very few small particles of old blood in the peritoneal cavity no evidence of damage was seen. In 18 autopsies no evidence of serious damage was found.*

four patients are known to have died, in 18 of which autopsy was performed.

The relative frequency of each biopsy diagnosis is shown in Table 2. These diagnoses were reported by 3 different pathologists and the diagnoses are unaltered, although cases were reviewed. There is a striking difference in both the diagnostic and unsuccessful biopsies before and after introduction of the special needles. The diagnosis of carcinoma is by far the most common and includes all slides in which the diagnosis of malignant

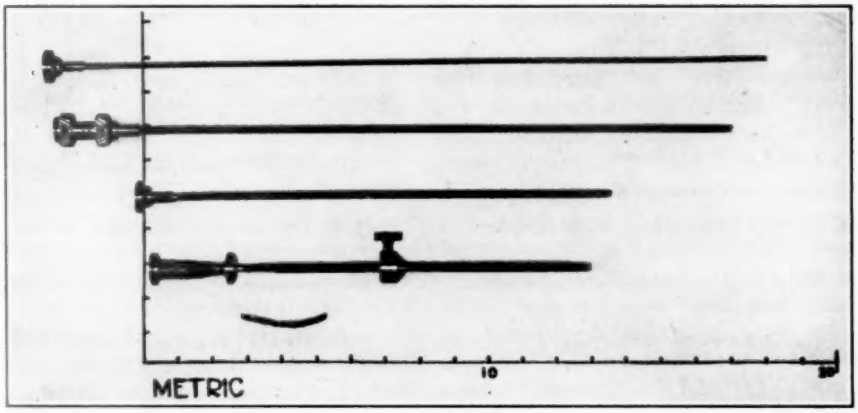


FIG. 1.—Roth-Turkel needle with gross specimen obtained. Scale is in centimeters.

Table 1 shows the number of biopsies done each year with the degree of success. Four of the liver biopsies done in 1943 were after the introduction of the special needles. The concomitant increase in utilization and percentage of success is easily seen. Biopsies were considered successful when an amount of liver tissue was obtained which was large enough for pathologic study. The period in 1945 includes only those up to July 15, 1945. The group included 52 men of whom 46 were white and 6 Negroes, and 21 women of whom 14 were white and 7 Negroes. Ages ranged from 21 to 79 years. Forty-

neoplasm was made. The most frequent of these was "partially differentiated adenocarcinoma metastatic to liver," but some were less specific—"undifferentiated carcinoma" or "malignant tumor" of the liver. The diagnosis of fatty metamorphosis was usually a secondary one in a case of tumor or cirrhosis but in a few instances it was the only diagnosis. A report of "consistent with Laennec's cirrhosis" usually stated periportal or focal fibrosis and chronic periportal hepatitis consistent with Laennec's cirrhosis if representative of the entire liver. An unequivocal diagnosis of Laennec's cir-

* In the biopsies which were done subsequent to this series, two accidents occurred. In one, bile was aspirated from the gallbladder which, as shown by subsequent autopsy, had been punctured by transfixing the anterior part of the liver. This was uncomplicated and had nothing to do with the patient's death. In the other, the duodenum was apparently penetrated, as the biopsy consisted of duodenal mucosa. There was no subsequent fever, tenderness, or disability. Such incidents, however, concretely illustrate the danger of the procedure and emphasize the care which should be taken with each attempt.

TABLE 2.—PATHOLOGIC DIAGNOSES FROM BIOPSY SPECIMENS BEFORE AND AFTER INTRODUCTION OF SPECIAL NEEDLES

Diagnosis	1939–43	1943–45	Total
Carcinoma (all types)	8	13	21
Consistent with Laennec's cirrhosis	0	8	8
Fatty metamorphosis	3	7	10
Laennec's cirrhosis	1	6	7
Biliary stasis	0	5	5
Hemosiderosis	0	3	3
Necrosis or degeneration	1	2	3
Acute hepatitis	0	3	3
Acute cholangitis	0	1	1
Fibrosis	0	1	1
Amyloidosis	0	1	1
Liver			
No pathologic diagnosis	2	4	6
Unsatisfactory	10	5	15

TABLE 3.—CORRELATION OF AUTOPSY AND BIOPSY DIAGNOSES

Biopsy diagnosis	Autopsy diagnosis
1939–1943	
1. Blood (2 biopsies)	Well-differentiated squamous cell carcinoma of esophagus with metastases
2. Tumor, liver and blood	Primary carcinoma of liver
3. Liver—no pathologic diagnosis	Focal fibrosis of liver
4. Partially differentiated adenocarcinoma	Partially differentiated squamous cell carcinoma of bronchus
5. Slight fatty metamorphosis; acini of columnar epithelium	Well-differentiated adenocarcinoma of liver—bile duct type
6. Carcinoma—type undetermined	Undifferentiated carcinoma of trachea with metastases
7. Laennec's cirrhosis	Laennec's cirrhosis
8. Normal glycogen storage	Fatty metamorphosis
1943–1945	
1 Hemosiderosis, slight chronic periportal hepatitis	Hemochromatosis; Laennec's cirrhosis
2. Partially differentiated adenocarcinoma metastatic to liver	Partially differentiated adenocarcinoma of body of pancreas
3. Undifferentiated carcinoma of liver	Undifferentiated carcinoma of the bronchus with metastases
4. Liver—no pathologic diagnosis	Passive hyperemia of liver
5. Fatty metamorphosis, marked; fibrosis consistent with clinical diagnosis of Laennec's cirrhosis	Probable primary carcinoma of liver: Laennec's cirrhosis
6. Focal fibrosis—consistent with Laennec's cirrhosis	Laennec's cirrhosis
7. Consistent with Laennec's cirrhosis	Laennec's cirrhosis
8. Secondary carcinoma of liver—probably squamous cell	Partially differentiated squamous cell carcinoma of esophagus with metastases
9. Laennec's cirrhosis, fatty metamorphosis	Laennec's cirrhosis
10. Undifferentiated carcinoma, fibrosis and atrophy, consistent with primary carcinoma of liver	Primary carcinoma of liver; Laennec's cirrhosis

rhosis was made when a sufficiently large sample was obtained to rule out subcapsular or focal fibrosis. The classification of acute hepatitis includes both periportal and diffuse types. The "unsatisfactory" cases are those in which sufficient tissue was lacking for a histologic diagnosis. Of the 5 unsatisfactory instances in the later group, 3 were in patients who subsequently had satisfactory biopsies.

The autopsied cases (Table 3) afford an opportunity to check the accuracy of the biopsy diagnoses. In the period 1939–1943, 4 may be considered to be correct, whereas in 2—bile duct carcinoma (No. 5) and focal fibrosis (No. 3)—the lesion was missed. The case of carcinoma of the esophagus metastatic to the liver (No. 1), in which only blood was obtained by biopsy, must be considered a gross error. The diagnosis of normal glycogen storage was undoubtedly correct but was not subject to check at autopsy because of postmortem tissue changes.

During the period from July 1, 1943, to 1945, 7 of the 10 biopsies may be considered correct and in 1, a carcinoma (No. 5), probably primary in the liver, was missed although the accompanying cirrhosis was correctly diagnosed. In the case of passive hyperemia diagnosed at autopsy (No. 4) there is question as to whether this change was present when the biopsy was taken. The biopsy diagnosis of hemosiderosis and slight chronic periportal hepatitis (No. 1) is not altogether satisfactory in the case of hemochromatosis, although it is consistent.

To assess the clinical value of these biopsies is difficult and at least in part subjective. When the charts were reviewed, the biopsies were considered worthwhile if they established a primary diagnosis or confirmed a clinical impression. If they were not in agreement with the general clinical picture but could not establish a diagnosis or were unsatisfactory biopsies, they were considered not helpful. In the early group, 13 of 26 attempted biopsies were helpful (50%). However, 13 of 16 successful biopsies were helpful (80%). In the latter period, 38 biopsies were helpful clinically. These constitute 71.6% of the total 53 cases or 79.2% of the 48 successful cases.

Of the 68 livers from which biopsies were taken, 31 were described as nodular or irregular, and of these 18 (58%) were diagnosed carcinoma by biopsy. Of the total, only 4 livers were not palpable and in 3 of these biopsy was successful.

Indications and uses of liver biopsy are somewhat limited but nevertheless important. It is felt as a result of experience gained in this series of cases that any case of hepatomegaly in which the etiology is questionable deserves a biopsy. Biopsies may be used in following the progress and evaluating the therapy of chronic hepatic disease such as cirrhosis. Investigation of the parenchymal changes in epidemic hepatitis,[3,13] toxic hepatitis, Weil's disease and other conditions may be greatly benefited by frequent biopsies during the course of the illness. Vital studies of living tissue obtained by human liver biopsy may aid materially in elucidating the normal physiologic function of the liver and its alterations in metabolic diseases. Generally, it is felt that only easily palpable livers should be needled. Although routine bleeding, clotting, and prothrombin times were not done in these cases, it is believed that they should be as an added precaution.

The intercostal approach advocated by some authors is not recommended. There is danger of tearing the liver should the patient inadvertently breathe while the needle is in the liver and held rigidly between the ribs. Acutely ill patients cannot coöperate well enough to permit the procedure, and needless transfixion of the pleural space may result in empyema, traumatic pneumothorax, or air embolism.

The use of peritoneoscopy in every case is not recommended. The procedure requires expert training and an expensive instrument and is therefore not widely available. In addition, in many cases it adds little to the biopsy procedure. In those cases in which the liver is not palp-

able or in which a nodule is suspected but cannot be felt peritoneoscopy may be valuable in guiding the biopsy needle. However, it is felt that routine peritoneoscopy adds needlessly to the risk in each case.

The 2 needles in current use at Cleveland City Hospital each have their advantages. The Silvermann instrument is smaller and yields smaller specimens, but it is easier to handle. The sections made from these specimens show a moderate amount of tissue distortion due to pressure. The Roth-Turkel needle is larger, yields larger specimens, and produces little or no distortion of tissue. It is a little more difficult to control than the smaller needle.

From the pathologist's standpoint needle biopsy of the liver has certain advantages and certain limitations. Cytology in a properly obtained specimen is usually superior to that obtained at autopsy for the specimen is obtained from the living organism and fixed with a minimum of autolysis. Studies of glycogen content, for example, are more exact than those of autopsy specimens. However, cytology may be very poor in those instances where there has been distortion by pressure or shredding. A second advantage of the procedure is that it permits observation at intervals during life. This offers information as to the pathogenesis of certain diseases and the effects of treatment. For example, in Case 2 repeated biopsies of a liver the seat of Laennec's cirrhosis showed, in the first instance, marked fatty metamorphosis and in the second none. This may be accepted as evidence in discrediting the classification of fatty cirrhosis as an entity separate from Laennec's cirrhosis.

The limitations of the procedure are those relating to the examination of limited material. Lesions may be focal and missed by random sampling. Furthermore, certain diseases by definition imply a diffuse change. For example, if a biopsy shows perilobular fibrosis, bile duct regeneration and alteration of lobular architecture, a diagnosis of Laennec's cirrhosis is made. Actually, it should be stated (as we have stated in some instances) that if the biopsy is representative of the entire liver, the diagnosis is Laennec's cirrhosis. Focal areas of atrophy and fibrosis can imitate the histology of Laennec's cirrhosis. This is particularly true of the so-called "capsular pseudocirrhosis."

In some instances the material offered for examination is limited, including only a portion of a lobule. In these instances a complete objective diagnosis may be unwarranted but it is still possible to contribute information which, taken with other clinical data, may aid in diagnosis. For example, in the case of hemochromatosis, discussed earlier in this paper (Table 3), the objective diagnosis of cirrhosis was not thought to be justified due to the limited material. The hemosiderosis (Fig. 8), however, was of the type and of the degree seen in hemochromatosis.

The diagnosis of tumors, likewise, has the limitations of inadequate material. This is especially true of the diagnosis of primary carcinoma of the liver. However, since the introduction of the Roth-Turkel needle, generous samples have been submitted and the histologic picture in many instances could not be greatly improved on by formal surgical biopsy.

Several cases are cited briefly to illustrate the use of liver biopsy.

Report of Cases. CASE 1. F. S., a 63 year old white man in whom a diagnosis of cirrhosis of the liver was made by surgical biopsy during laparotomy in 1943, was admitted to the medical service of the Cleveland Clinic Hospital May 2, 1945, complaining of swelling of the abdomen and ankles, weakness and shortness of breath of 2 months duration. Examination revealed a distended abdomen with dilated superficial veins. A fluid wave and shifting dullness were present. The liver, which was enlarged to 5 cm. below the costal margin, was quite hard. There was 1 nodule about 4 or 5 cm. in diameter palpable at the edge. Biopsy (Fig. 2) done on May 3 revealed "Laennec's

cirrhosis, slight periportal hepatitis." Repeat biopsy on July 13 showed little change.

CASE 2.—F. Z., a 29 year old white man was admitted to the medical service March 8, 1945, complaining of pain and swelling in the abdomen, malaise and fever. Examination revealed a distended, tender abdomen with a large, firm liver felt at the level of the umbilicus. Biopsy (Fig. 3) March 12 revealed Laennec's cirrhosis with fatty metamorphosis and acute hepatitis. After symptomatic and supportive therapy, repeat biopsy (Fig. 4) on May 16 showed disappearance of the fatty metamorphosis and acute hepatitis. The patient was clinically much improved and the liver was much smaller than previously.

CASE 3.—C. G., a 59 year old white man was admitted to the surgical service May 31, 1945, with a history of chronic draining empyema for many years. Examination revealed a smooth, firm, markedly enlarged liver. Biopsy (Fig. 5), June 19, was reported "moderate amyloidosis of liver."

CASE 4.—J. S., a 59 year old white man was admitted to the medical service July 16, 1945, with indefinite history of abdominal pain for 2 months and a weight loss of 30 pounds in the past year. There were signs of atelectasis in the left upper lung field and several firm, 1 to 2 cm. cervical lymph nodes. The liver, which was 10 cm. below the right costal margin, was hard, nodular and tender. Biopsy (Fig. 6) on July 24 showed undifferentiated carcinoma of the liver of unknown origin. Subsequently autopsy revealed an undifferentiated carcinoma of the upper lobe of the left lung and widespread metastases to the liver and cervical and mediastinal lymph nodes (Fig. 7).

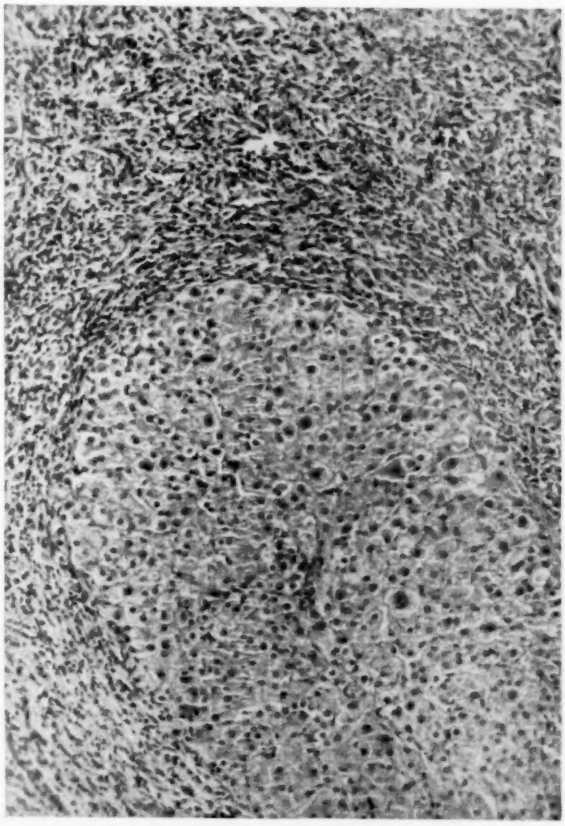


FIG. 2.—(S–33281) L. P. Advanced Laennec's cirrhosis—note lobule surrounded by fibrous tissue which contains many new bile ducts and shows slight round cell infiltration.

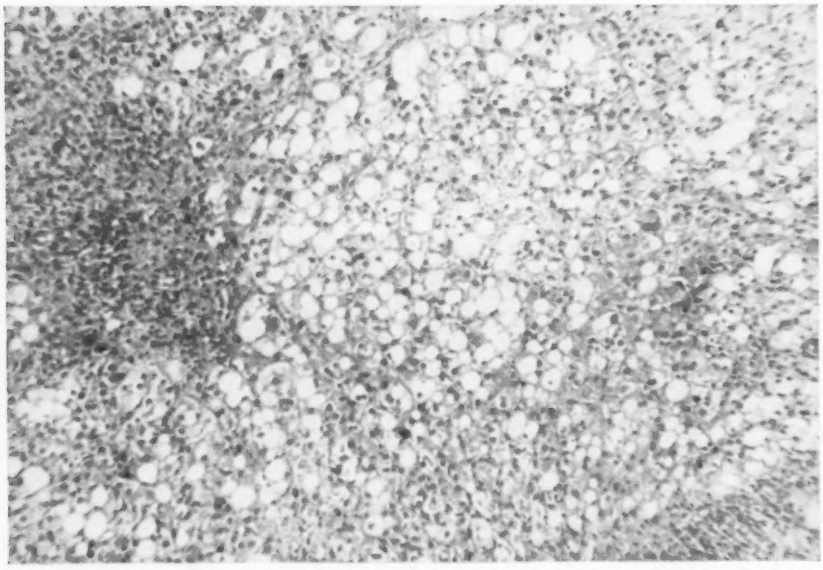


FIG. 4.—(S–33366) L. P. The same patient as (S–33033) showing disappearance of fatty changes and acute hepatitis.

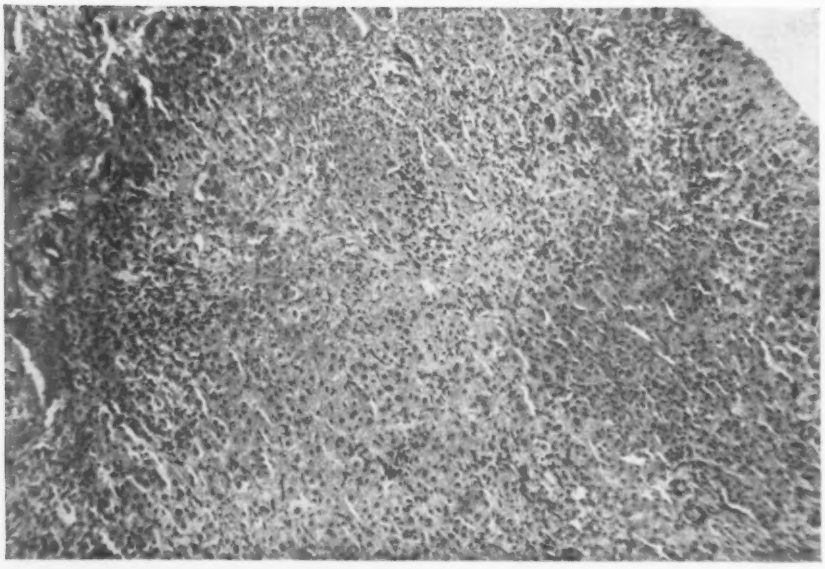
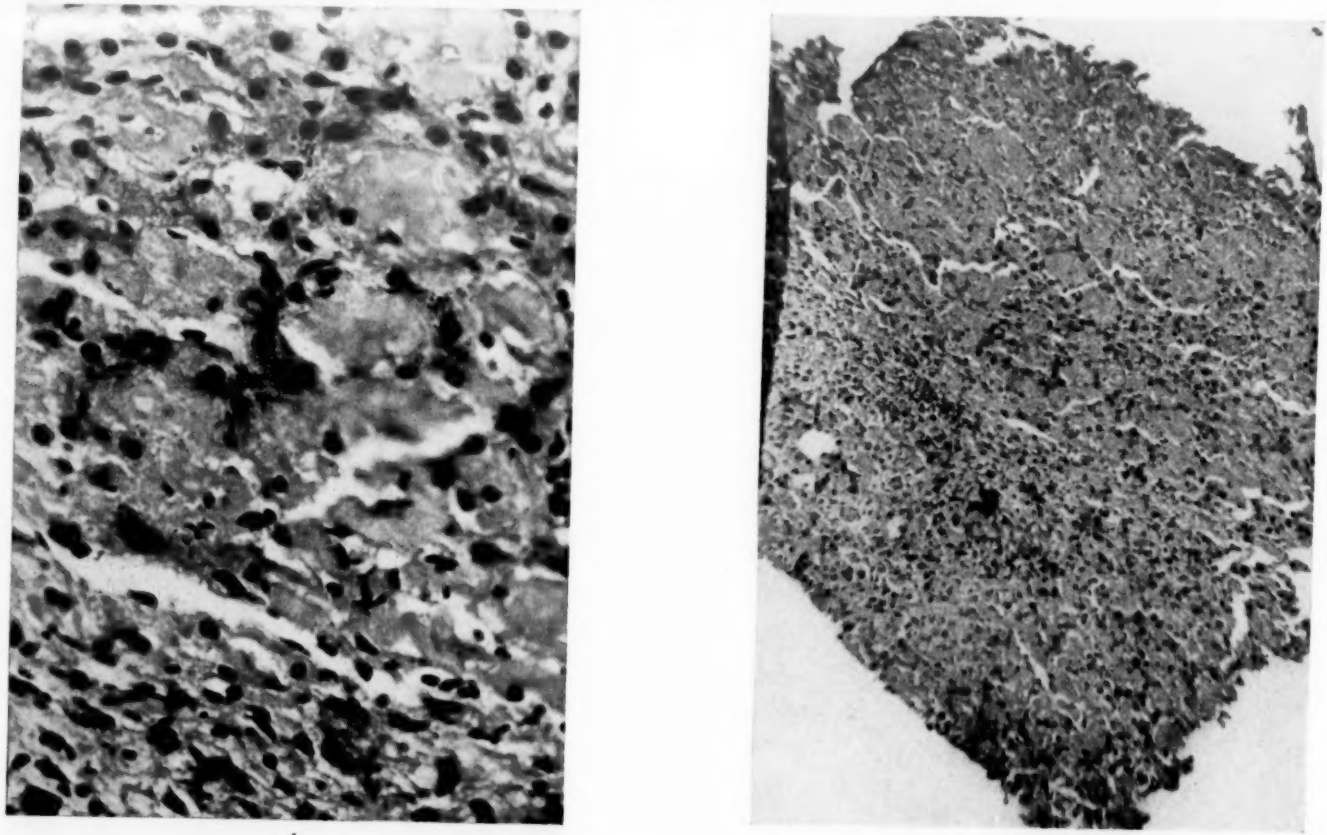


FIG. 3.—(S–33033) L. P. Liver, the seat of Laennec's cirrhosis showing also acute hepatitis and marked fatty metamorphosis.

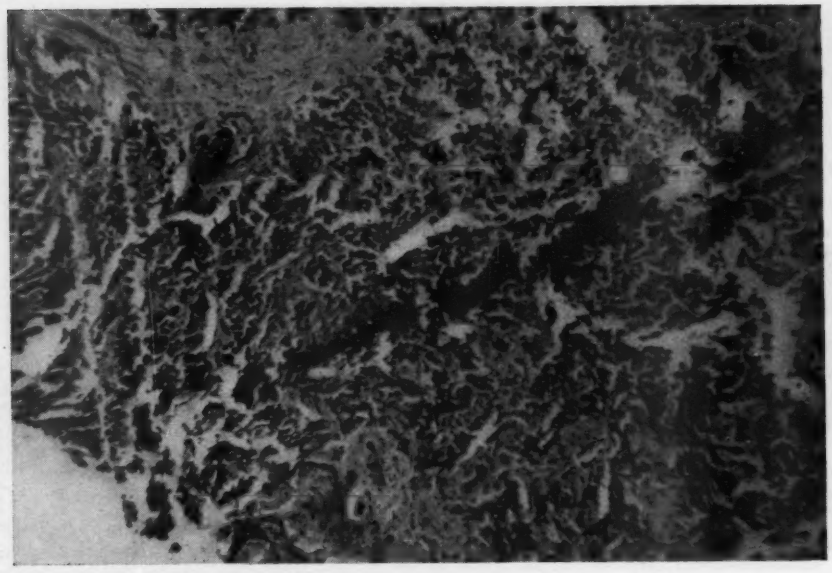
hosis showing also acute hepatitis and marked fatty metamorphosis.

showing disappearance of fatty changes and acute hepatitis.

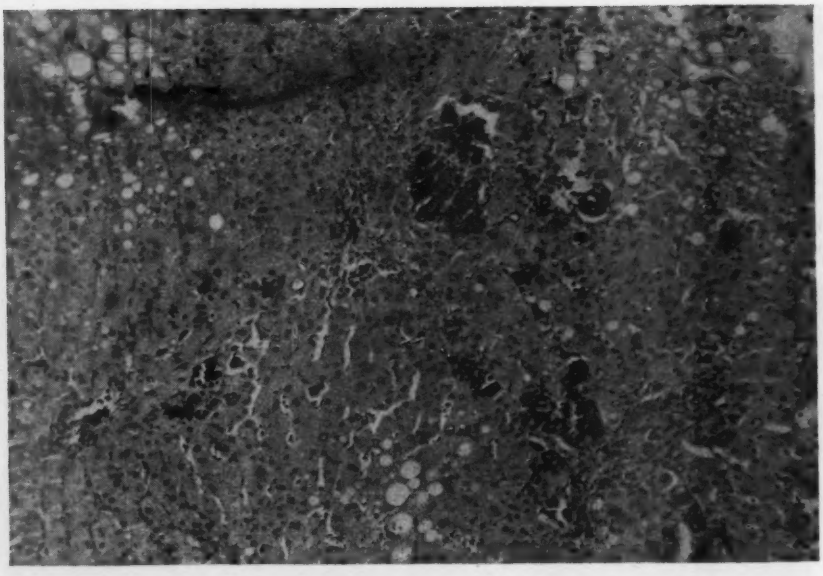


A *B*

FIG. 5.—(S–33516) L. P. and H. P. *A* and *B*, Amyloidosis of liver.



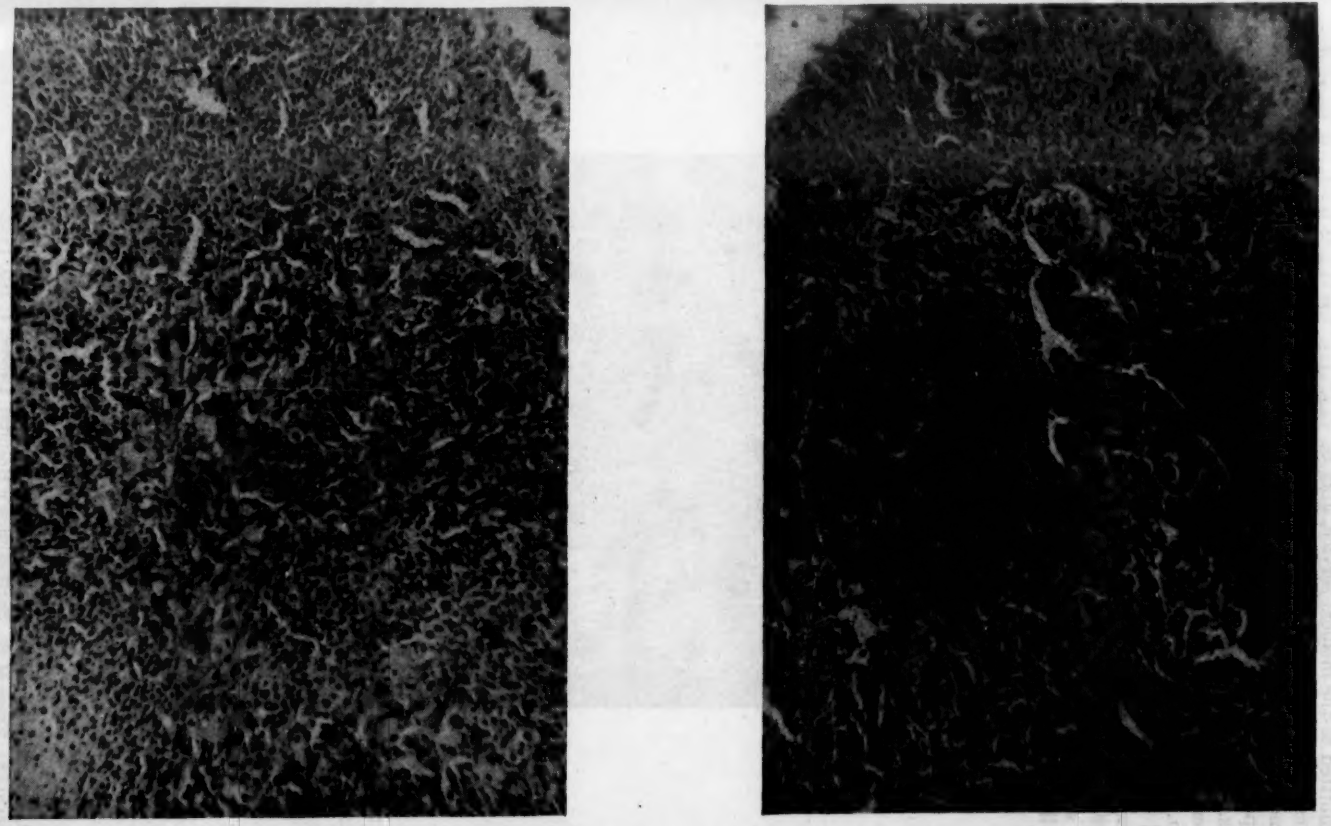
B



A

FIG. 6.—(S-33674) L. P. *A*, Metastatic undifferentiated carcinoma of the liver. At autopsy, the primary site was found to be in the left bronchus. *B*, Another area from the same biopsy.

FIG. 6.—(S–33674) L. P. *A*, Metastatic undifferentiated carcinoma of the liver. At autopsy, the primary site was found to be in the left bronchus. *B*, Another area from the same biopsy.



A *B*

FIG. 7.—(S–33580.)–*A*. and *B*, Two areas of primary carcinoma of the liver with atrophy and fibrosis.

CASE 5.—E. V., a 59 year old white man, was admitted to the medical service, July 5, 1945, complaining of pain in the abdomen of 1 month's duration followed in 1 week by appearance of a mass. He had lost 25 pounds. Examination revealed a hard, nodular liver extending 10 cm. below the costal margin. Biopsy (Fig. 7), July 6, was reported undifferentiated carcinoma of the liver with atrophy and fibrosis consistent with primary carcinoma of the liver. Necropsy showed nodular, primary carcinoma of the liver.

Summary and Conclusions. Needle biopsies of the liver have been done on 68 patients in Cleveland City Hospital since 1939. Biopsies have been most useful in the diagnosis of cancer of the liver and in establishing the nature of diffuse parenchymal liver disease including cirrhosis. The occasional fatalities reported by others have so far not been encountered in this series.

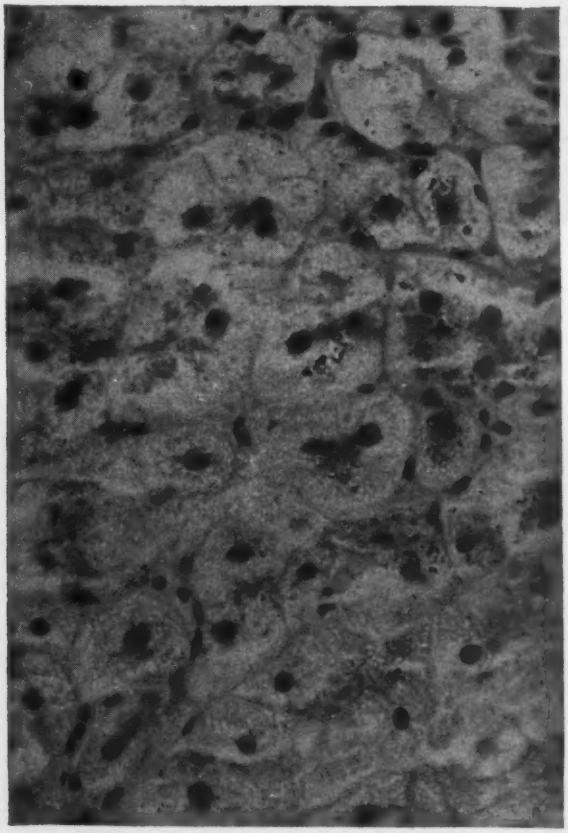


FIG. 8.—(S–32371.) Hemosiderosis of liver from a case of hemochromatosis.

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PLASMA PROTEINS

I. Alteration in Diabetic Retinitis

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The purpose of this paper is to report studies made on 31 patients with diabetic retinitis. The work was done chiefly to determine any correlation between certain alterations in the plasma proteins and retinal changes and to determine whether a high protein intake would alter either or both of these disorders.

Previous studies[3] have shown that the plasma protein pattern (Tiselius technique) is frequently abnormal in diabetes mellitus when the condition is inadequately treated. The typical change found in the protein fractions was a reduced level of albumin and an increase in β globulin. The total quantity of protein may be normal or only slightly reduced. In such cases the levels of the plasma proteins can be restored to normal by adequate treatment of the diabetes if complications such as infection, renal insufficiency or retinitis are not present. In cases of diabetic retinitis restoration of the plasma protein levels to normal was brought about with much more difficulty. Higher protein diets were required and the change was much slower. In instances in which renal disease and albuminuria were present in addition to the retinitis, the plasma protein abnormalities were not always corrected by the methods employed.

The term, "adequate treatment," as used in this paper, means a careful attempt to maintain the patient in normal strength and at or near ideal weight, to maintain as far as possible the urine free from sugar at all times, normal blood sugar levels both fasting and 4 hours after meals, and a normal total blood cholesterol level.

Methods. Longsworth's modification[5] of the Tiselius electrophoretic method was used to estimate the albumin, α globulin, β globulin, γ globulin, and fibrinogen in the plasma. Phosphate buffer solution of pH 7.8, ionic strength 0.16 was employed. Normal values determined in this laboratory on 21 subjects have been reported.[3] A more complete description of the method as employed is given in our previous paper.[1] Total protein values were determined by Pregl's modification of the micro-Kjeldahl method for estimating total and non-protein nitrogen.

Urea clearance tests of kidney function were done by the technique of Moller, McIntosh and Van Slyke.[6]

Results. A number of factors were used to evaluate these 31 cases of diabetic retinitis. These factors included sex and age distribution, duration of the diabetes, presence or absence of proteinuria, of hypertension and of reduced urea clearance values, adequacy of treatment, total duration of such treatment, protein intake, electrophoretic analysis of plasma proteins and progress of the retinal changes.

An analysis of the sex distribution reveals that diabetic retinitis is more common in women than in men. Of the total of 31 patients, 26 (84%) occurred in women and 5 (16%) in men (Table 1). The high incidence of diabetic retinitis in women also characterized Bedell's series.[5] This is in contrast to the almost equal distribution of diabetes mellitus in the 2 sexes.

Age is also an important factor; 25 patients (80%) were between 40 and 70 years of age (average 51) (Table 1).

The average duration of the diabetes

for both sexes as judged by the history was 11 years. In contrast, the symptoms assumed to designate the onset of retinitis were of relatively recent origin. Diabetic retinitis in men was not recognized until diabetes had been present from 12 to 25 years (average 19) and in women until diabetes had been present for 2.5 to 22 years (average 10).

Proteinuria was common when the diabetes was untreated but often disappeared during adequate management. A trace of albumin was observed in 13 patients initially, but disappeared during management in 5 of the 11 who had subsequent urinalyses.

occasionally at intervals of 2 or 3 months. The urinalyses made at home seldom showed glycosuria. Each reëxamination of the patient included blood and urine sugar determinations fasting and 3 or 4 hours postprandially at noon and occasionally 3 or 4 hours postprandially in the afternoon. An effort was made to maintain blood sugar levels at normal levels, and only occasionally was the attempt unsuccessful. In a few instances isolated blood sugar levels were as much as 40 mg. % above normal. Normal levels are taken to be 80 to 120 mg. per 100 ml. of venous blood, Myers-Bailey method.

TABLE 1.—AGE AND SEX DISTRIBUTION IN CASES OF DIABETIC RETINITIS STUDIED

Age (yrs.)	Men	Women	Total
20–29	1	1	2
30–39	1	0	1
40–49	1	5	6
50–59	0	12	12
60–69	2	5	7
70–79	0	3	3
Total	5	26	31

Hypertension was present in approximately half of the group; 17 (55%) had a systolic blood pressure of 150 mm. of mercury or more; 13 (42%) had a diastolic blood pressure of 90 mm. of mercury or more.

Urea clearance tests were done in 9 patients. In 5, clearance values averaged 80% or more, and of these all but 1 showed persistent proteinuria. The remaining 4 patients had urea clearance values of 20, 30, 36 and 64% respectively. The blood urea was elevated above 55 mg. per 100 ml. in 3 patients who did not have urea clearance determinations.

Adequate treatment for a number of months was obtained in 10 patients who will be discussed in greater detail. These patients were specially selected as individuals who maintained excellent diabetic control throughout the period of study. Each patient made urinalyses at home 3 or 4 times daily and had blood sugar levels determined at monthly intervals or

In this group of patients the protein intake was varied from time to time and the effects were correlated with shifts in their plasma protein patterns.

Total Plasma Proteins. We have found the normal total plasma protein[4] to range from 5.9 to 7.8 gm. per 100 ml. with an average of 6.5 gm. The initial total protein was within this range or only slightly below in 29 patients. The remaining patients had advanced renal disease. The initial total protein values in these 2 instances were 4.8 and 5.3 gm. per 100 ml.

Albumin Fraction. The normal range for albumin fraction[4] was 3.7 to 5.1 gm. per 100 ml. with an average value of 4.1 gm. The plasma albumin level was low in 28 (90%) of the 31 patients. The individual determinations ranged from 2.06 to 3.8 gm. per 100 ml. with an average of 3.2 gm. The lowest values were obtained in 4 patients with impaired renal function. The 3 remaining patients with normal albumin levels were all under ade-

quate management from 3 to 19 months before the first determinations were conducted.

β Globulin Fraction. The normal range of β globulin determined in 25 normal controls in our laboratory[4] were 0.65 to 1.07 gm. per 100 ml.; the average was 0.81 gm. Of the 31 patients, 29 (93%); demonstrated an elevated β globulin fraction; the average was 1.29 gm. per 100 ml.

Let us now consider the effects of variation in protein intakes upon the plasma protein level in the 10 carefully selected patients who can be considered as having received adequate treatment. Plasma proteins were subjected to electrophoretic analysis repeatedly in these 10 patients. Four of the 10 received relatively low daily protein intakes. One of the 4 with a low albumin level initially maintained an intake of 50 gm. protein per day for 10 months. A further fall in plasma albumin level occurred. The plasma albumin of another patient increased to nearly normal levels while receiving 80 gm. protein per day for 3 months. The remaining 2 patients, who had received 77 and 84 gm. of protein per day for 10 days and 5 months respectively, showed no alteration in plasma albumin levels.

The other 6 of this group were given a much larger daily protein intake, chiefly as meat, for a period ranging from 3 weeks to 6 months. Four of the 6 had a significant elevation in albumin fraction at the end of the test period. One of these 4 had a normal albumin level 3 months after the protein intake was increased from 70 to 140 gm. per day. Two others showed a significant rise in this same fraction 3 weeks and 6 weeks after protein intakes were elevated by 40 gm. per day to 120 and 140 gm. respectively. The albumin fraction in the fourth patient gradually returned to normal 6 months after the protein intake was increased from 76 to 136 gm. per day.

In the remaining 2 patients given a high protein intake, the albumin levels failed to increase over a period of 3 months and 1 year respectively. The protein in the diet was raised from 60 to 140 gm. daily in 1 and from 60 to 120 gm. per day in the other. Persistent proteinuria was present in each patient, but urea clearance values were not obtained.

No case was seen demonstrating a fall in plasma albumin when more protein was prescribed in the diet. In most instances where albumin levels became normal, β globulin levels approached normal.

The 4 patients who were regarded as improved showed the following course of events: the first patient entered the period of study with concentric contraction of both form and color fields in the right eye and vision was 6/12–1. There was loss of the inferior half and partial loss of the temporal and nasal superior form fields in the left eye. In addition, concentric contraction of color fields was observed. Vision was 6/30–1. One year later central fields were normal. Ophthalmoscopic examination on 5 occasions showed no retinal hemorrhages (Case 1, Table 2).

The second patient originally had a loss of green color field and a relative central scotoma for blue in both eyes. Several months later the green field was normal and the central scotoma had disappeared. Two small scotomas in the central field of the right eye persisted. The left central field was normal when first tested and remained unchanged. No new hemorrhages appeared. Visual acuity measured 6/9–1 in both eyes at the beginning and the end of the period studied (Case 2, Table 2).

There were no new hemorrhages in the 2 remaining patients during a 6 month and 2 year period of observation. Subjectively, vision was improved, but no actual measurement was obtained.

Discussion. Patients with uncomplicated diabetes mellitus may have low plasma albumin levels when untreated or poorly treated. Adequate treatment of the diabetes was almost invariably accompanied by a prompt return to normal of the albumin level. The diet needed

only to contain 1 gm. of protein per kg. body weight.

Patients with uncontrolled diabetes accompanied by retinitis had much lower plasma albumin levels and higher β globulin levels than were observed in the uncomplicated cases. With adequate treatment of the diabetes the protein levels were improved but not restored to normal unless the diet contained a high daily protein intake. Proteinuria apparently accentuated the hypoproteinemia and the albumin fraction was not restored to normal by increasing the protein in the diet.

Table 2.—Tiselius Protein Fractionation on 2 Patients—Changes Observed on Repeated Studies After Increased Protein Intake

	Diet			Observation period							
Case	C	P	F	From	To	Date	Total protein	Alb.	α Glob.	β Glob.	γ Glob.	Fibrinogen
1	130	56	130	2/ 3/43	11/30/43	10/ 8/43	6.12	3.37	0.36	1.37	1.02	
						11/30/43	6.28	2.85	0.39	0.64	0.77	0.63
	130	80	120	11/30/43	12/20/43	12/20/43	6.42	4.03	0.53	0.76	0.61	0.49
2	100	71	50	3/15/44	6/16/44	6/16/44	6.54	3.43	0.38	1.26	1.12	0.38
	100	100	50	6/22/44	8/ 1/44	8/ 1/44	6.70	3.56	0.30	1.37	1.20	0.36
	100	140	50	8/ 1/44	9/25/44	9/25/44	7.10	3.99	0.28	0.92	1.24	0.57

Both patients showed: (1) gradual rise in total protein; (2) gradual rise in total albumin; (3) gradual fall in tota β globulin.
During the interim of study visual fields improved, visual acuity improved, and the retinæ showed fewer hemorrhages. Neither patient had albuminuria or measurable impairment of renal function.

The greatest improvement in retinal changes occurred in those patients in whom high protein intake restored the plasma protein pattern to normal. This observation suggests the value of diabetic diets of high protein content as an adjunct in the prevention or treatment of diabetic retinitis. It is evident, however, that a much larger series must be studied over a longer period of time before final conclusions regarding the therapeutic value of high protein intake in cases of diabetic retinitis can be drawn.

Summary. 1. Plasma proteins in patients with diabetic retinitis are characterized by low albumin, high β globulin and a tendency toward normal total protein values.

2. Adequate management of the diabetes when diets contained a maintenance amount of protein improved but did not correct the plasma protein pattern in patients having retinitis.

3. When adequate treatment was instituted and the daily protein intake increased to 120 to 140 gm., the plasma protein pattern either improved or returned to normal, provided serious renal disease was not present.

4. The 4 patients in whom high protein diets restored the plasma proteins to normal showed the greatest retinal improvement.

5. From these studies, it appears that a high protein diet may be a useful adjunct in the management of diabetic retinitis.

We wish to express our sincere appreciation to Dr. A. D. Ruedemann and Dr. Jacob Moses for their coöperation in following the retinal changes and to Mr. James Clark for performing many of the analyses.

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THE FALLACY OF THE EXTON-ROSE GLUCOSE TOLERANCE TEST

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It is the purpose of this paper to present information from the literature which indicates that the Exton-Rose 2 dose, 1 hour, glucose tolerance test is based upon a physiologic misconception. In addition, the results of a series of well-controlled glucose tolerance tests are presented to support further this contention.

In a previous paper 1 of us[9] reviewed the pertinent literature and pointed out certain discrepancies which indicated that the Exton-Rose test was less reliable than the conventional 1 dose test. Since 1942, 2 additional studies[16,21] on the Exton-Rose test are worthy of note and indicate that this test is still considered a worthwhile procedure. The use of 2 doses of glucose, one initially and the second ½ hour later, as employed in the Exton-Rose test[5] was inspired by the paradoxical law of Allen[1] which states that the more sugar given to a normal individual, the more it is utilized and that the limits of tolerance in normal individuals are apparent rather than real. Therefore, there is no real limit to the ability of a normal person to utilize glucose. The above is exemplified by the Hamman-Hirschman effect[8] in which the resultant peaks in the blood sugar curves become progressively lower after successive doses of glucose. Exton and Rose[5] believed that if 50 gm. of glucose were given orally and then followed in ½ hour by a similar dose a paradoxical result would occur in that the blood sugar would either fall in the second ½ hour of the test or at most fail to rise appreciably. In arriving at the conclusion that a second 50 gm. dose of glucose would have any appreciable effect upon the blood sugar curve in the short space of ½ hour, Exton and Rose failed to take into consideration certain physiologic facts, namely: (1) the rate of absorption of glucose from the gastro-intestinal tract, (2) its rate of utilization, and (3) the natural shape of a glucose tolerance curve after giving 100 gm. of glucose, whether it is given in 1 dose or in divided doses of 50 gm., at ½ hour intervals. Let us consider each of these factors in turn.

With regard to intestinal absorption, it has been estimated by Cori and Cori,[4] after a comprehensive review of the literature, that the maximum rate of absorption from the gastro-intestinal tract in man is 0.85 gm. per kilo, or about 60 gm. per hour for an average sized man. Actual measurements of absorption by Warren, Karr, Hoffman and Abbott[20] in man indicate that the maximum rate of absorption is 43 gm. per hour and usually less than this. Thus, the Exton-Rose test supplies twice as much glucose as the gastro-intestinal tract is capable of absorbing in 1 hour. In other words, it adds 50 gm. of glucose to the stomach while there is still an excess in the upper intestinal tract. Groen[7] concludes that the absorption of a glucose test meal of 50 gm. would be 4 hours or somewhat less. We think that this is too conservative. Groen believes that if the glucose were introduced directly into the whole intestine a greater absorption would occur, but that when glucose is given by mouth the pylorus takes care that absorption does not take place at a rate which

exceeds the capacity of the storage mechanism. The latter portion of this statement is in keeping with the result of Ravdin, Johnston and Morrison,[14] who found that when glucose solutions of varying concentrations from 3.5 to 50% are placed in the stomach, the concentrations obtained from the jejunum and ileum at the end of 1 hour are remarkably constant and did not exceed 5.3%. Thus, the stomach protects the intestine from receiving too much glucose in too great concentrations.

The following pertinent excerpt is quoted from Peter's and Van Slyke's "Quantitative Clinical Chemistry:"[13] "Apparently the mechanism for the utilization of sugar by the tissues is not greatly accelerated until the blood sugar reaches a certain height. The activity of the mechanism increases as the blood sugar rises higher, until, at the peak of the curve, utilization rate overtakes, and then surpasses the absorption rate, in spite of the fact that the absorption may still remain at its maximum. The accelerated utilization, once speeded up, does not stop until the blood sugar has become subnormal. As shown by Cori, absorption from the intestine cannot surpass a certain maximum rate; if more glucose is ingested beyond the amount eliciting complete absorption activity, absorption continues for a longer time, but not at a faster rate. Consequently, when glucose utilization is stimulated to outrun this maximum inflow, the blood sugar begins to fall from its peak, and continues to do so even though the intestine is still loaded with glucose."

In view of the above passage it would seem pointless to give a second dose of glucose at the height of the blood sugar curve, since in a normal individual the curve would fall whether a second dose were given or not given. In a diabetic the curve would continue to rise whether 1 initial dose or 2 doses at ½ hour intervals were given. Therefore, any difference in the effect which the administration of 1 dose of 100 gm. or 2 doses of 50 gm. each would have upon the blood sugar curve would not be manifested during the 1st hour or the duration of the entire Exton-Rose test.

Relative to the maximum rate of glucose utilization, experience has shown that 25 to 30 gm. of glucose is optimal for the 1 hour intravenous tolerance test.[11,19] This direct introduction of a sizable quantity of glucose into the blood stream provides a much more intense stimulus to the glucose disposal mechanism than the slow absorption after oral administration. The fact that the body requires 1 hour to dispose of 25 gm. of glucose given intravenously, thereby producing the maximum stimulus, makes it seem unlikely that the disposal of an oral dose of 50 gm. could occur in ½ hour and any appreciable response be manifested to a second dose of 50 gm.

The final factor concerns the natural shape of the oral glucose tolerance curve. It is well known that in the glucose tolerance test in normal people the peak of the curve, depending on absorption and utilization, will usually occur between 30 and 60 minutes. If absorption and utilization of glucose are such that the curve rises slowly, the peak will probably occur at 60 minutes. On the other hand, if absorption is more rapid and utilization less so during the first 30 minutes, the peak will occur more abruptly, the glucose disposal mechanism will be sharply stimulated, and the curve will fall during the second ½ hour. We believe these phenomena will occur regardless of whether the glucose is given in 1 dose of 100 gm. or in divided doses of 50 gm., as demonstrated in our series of parallel glucose tolerance tests in the same individuals shown in Table 1.

Method. Ambulatory patients on the medical service were used for this study. These patients were afebrile, with mild non-disabling diseases, and had been prepared by generous antecedent carbohydrate diet since the importance of the last-mentioned factor has been repeatedly demonstrated.[3,10,17,18] A 12 hour rest and fast pre-

ceded each test. The tests were done within 2 to 5 days of each other. The general condition, activities and emotional status of the patient were observed and it is believed that these were practically constant for several days prior to the performance of each pair of tests in a given individual. Venous bloods were taken at exact times by 1 of 2 individuals highly skilled in venepuncture with minimum use of a tourniquet and the blood sugar was determined in duplicate on each specimen according to the method of Folin and Wu using a photoelectric colorimeter. In 5 cases, the 1 dose test was performed before the 2 dose test and *vice versa* in the other 5, since it has been shown by Lennox[11] that repeated blood sugar curves on non-diabetic individuals on successive days are progressively lowered.

Table 1.—A Comparison of the Results in the 1 Dose Glucose Tolerance Test and the Exton-Rose Test in the Same Individuals

(In each instance, the 1 dose test is listed first)

Case No.	Days between tests	Fasting (mg./100 cc.)	30 min. (mg./100 cc.)	60 min. (mg./100 cc.)	90 min. (mg./100 cc.)	120 min. (mg./100 cc.)	Differences between 2nd and 3rd specimen
1	2	98	135	139	99	93	+ 4
		88	122	144	140	94	+22
2	2	78	124	97	102	80	−27
		97	107	119	93	98	+12
3	5	76	123	110	105	59	−13
		78	118	110	86	79	− 8
4	2	83	120	108	88	79	−12
		87	101	93	76	98	− 8
5	2	90	128	136	122	96	+ 8
		94	142	127	100	92	−15
6	2	84	130	100	99	90	−30
		78	121	110	87	85	−11
7	2	78	140	112	90	86	−28
		74	144	146	96	79	+ 2
8	2	79	128	116	85	98	−12
		80	122	143	92	103	+21
9	4	74	114	119	104	90	+ 5
		80	110	115	94	89	+ 5
10	2	78	117	101	99	92	−16
		100	146	123	100	109	−23

The results of the 2 tests are set forth in Table 1. It will be seen that the fall in blood sugar in the second ½ hour after the second dose of glucose in the 2 dose test is manifested only 5 times, whereas in the 1 dose test it occurs 7 times. Table 2 is a summary of the data from the last column of Table 1 showing the difference between the 30 and 60 minute blood sugar values. Table 2 shows that in the 1 dose test 3 cases had an average rise of 6 mg. per 100 cc., whereas 7 cases had an average fall of 20 mg. per 100 cc.; while in the 2 dose test 5 cases had an average rise of 12 mg. per 100 cc. and 5 cases had an average fall of 13 mg. per 100 cc. Thus it is obvious that the blood sugar curve in the 2 dose test of Exton and Rose does not fall in the second ½ hour following the second dose of glucose any more frequently than in the 1 dose test. This result is in direct contradiction to that of Exton and Rose who based their concept upon their finding that the blood sugar almost invariably fell after the second dose of glucose. A review of the literature reveals 2 additional series in which actual blood sugar values for both the 1 dose and 2 dose tests in the same individuals are available for comparison.[2,16] Review of these figures reveals results similar to our own series, and data

calculated by us from these figures are set forth in Table 3. These data lead to the same conclusions as our own which is shown in Table 2 and add further confirmation to our thesis that the Exton-Rose test is based upon a misconception.

Magath and Berkson,[12] and a rise of 30 mg. per 100 cc. is allowed in the second ½ hour by Gould, Altshuler and Mellen.[6]

In view of the data presented it is obvious that the 2 dose, 1 hour test follows the same type of curve as the con-

TABLE 2.—SUMMARY OF THE DIFFERENCES IN THE BLOOD GLUCOSE VALUES BETWEEN THE 30 AND 60 MINUTE SPECIMENS IN THE SAME INDIVIDUALS (AUTHORS' PRESENT SERIES)

	1 dose test			Exton-Rose test		
Behavior of blood glucose	No. cases	Average rise (mg./100 cc.)	Average fall (mg./100 cc.)	No. cases	Average rise (mg./100 cc.)	Average fall (mg./100 cc.)
Rise	3	6	..	5	12	
Fall	7	..	20	5	..	13

TABLE 3.—SUMMARY OF THE DIFFERENCES IN THE BLOOD GLUCOSE VALUES BETWEEN THE 30 AND 60 MINUTE SPECIMENS IN THE SAME INDIVIDUALS

	1 dose test			Exton-Rose test		
Behavior of blood glucose	No. cases	Average rise (mg./100 cc.)	Average fall (mg./100 cc.)	No. cases	Average rise (mg./100 cc.)	Average fall (mg./100 cc.)
Rise	4	+18	..	5	+15	
Fall	5	..	−23	4	..	−21
Rise	3	+23	..	7	+33	
Fall	7	..	−19	3	..	−39

First and second lines calculated from Brown (Med. Bull. Vet. Admin., **16** 152, 1939; calculated from Groups II and IV: normal individuals).

Third and fourth lines calculated from Spellberg and Leff (J. Am. Med. Assn., **129**, 246, 1945; calculated from Table 2).

Discussion. It is believed that sufficient evidence has been presented to prove that the Exton-Rose 2 dose, 1 hour glucose tolerance test does not differ physiologically from the conventional 1 dose oral glucose tolerance test using the same total dose of glucose. It is believed that it is misleading to consider the Exton-Rose 2 dose test as a separate entity. While Exton and Rose originally found that a majority of their blood sugar curves fell during the second ½ hour after divided doses of glucose, this was not substantiated by others. The original criteria of Exton and Rose which required a fall or no rise of the blood sugar in the second ½ hour of the test have been discarded in favor of criteria which do permit a considerable rise.[6,12] This fact in itself would seem to vitiate the original concept of the Exton-Rose test. A single 1 hour blood sugar value of 160 mg. per 100 cc. has been adapted as a criterion by Matthews, ventional 1 dose oral glucose tolerance test and the maximum permitted value at 1 hour in both tests is about the same. Thus, the original rise or fall phenomenon stressed by Exton and Rose and based on the paradoxical law of Allen ceases to be a determining factor. We believe that the crux of the matter is that the paradoxical law of Allen cannot operate (for the reasons previously set forth) in the short space of 1 hour when as large a dose as 50 gm. of glucose is given initially and again at ½ hour.

In the diabetic the blood sugar will rise sharply during both the first and second ½ hour of the test whether 1 dose of 100 gm. or 2 doses of 50 gm. are given. In the normal individual (whether 1 dose of 100 gm. or 2 doses of 50 gm. of glucose are given) the blood sugar curve may rise or it may fall in the second ½ hour depending upon the speed with which the peak level is reached and upon the speed with

which the glucose regulating mechanisms become fully mobilized.

The reason for disagreements between the 1 hour, 2 dose and the conventional 1 dose test is that the criteria for the short 2 dose test are established at or near the peak of the blood sugar curve while the criteria for the longer test are usually judged most heavily at the 2 or 3 hour level when the glucose disposal mechanism is reaching equilibrium again. If experience demonstrates that the 1 hour level of a glucose tolerance test is superior to the 2 or 3 hour levels in diagnosing diabetes or other abnormalities of glucose metabolism, then this factor of the time for collecting the critical blood specimen is the important decision and not the giving of 100 gm. of glucose at once or in 2 closely spaced doses at as little as ½ hour interval. At the present the weight of evidence does not favor the use of the peak value as the principal criterion but emphasizes the importance of using the 1 dose glucose tolerance test and following the blood sugar curve for 2 to 3 hours.[15]

Conclusions. 1. After giving 100 gm. of glucose in 1 initial dose the blood glucose curve is essentially the same as that obtained after giving 100 gm. in 2 divided doses of 50 gm. initially and 50 gm. at ½ hour (Exton-Rose procedure).

2. The absorption of glucose from the gastro-intestinal tract and the response of the glucose regulating mechanism is not sufficiently rapid to permit a paradoxical response in the short space of ½ hour. This is contrary to the hypothesis of Exton and Rose.

3. In view of the above 2 paragraphs, the physiologic hypothesis upon which the 2 dose, 1 hour (Exton-Rose) glucose tolerance test is based is unsound. The Exton-Rose test is not a separate physiologic entity and is not basically different from the 1 dose glucose tolerance test.

4. The interruption of the oral glucose tolerance test at 1 hour and the consequent use of the peak value as the principal criterion is much less accurate than the use of the 2 or 3 hour value of the glucose tolerance curve.

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ANALYSIS OF INCIDENCE AND CAUSES OF DEATH IN AN ACUTE PSYCHOPATHIC HOSPITAL

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This is a study of the causes of death in patients admitted to the Psychopathic Department of the Philadelphia General Hospital, from August 1943 to August 1944. In order better to understand this analysis, it is desirable to describe the type of patient admitted and the method of admission. The Psychopathic Department receives psychotic and unmanageable patients from all departments of its own hospital and any other hospital in the city which is unable to handle them, in addition to its own direct admissions. This applies particularly to senile patients who may get periods of agitation, forgetfulness, confusion, etc., when it is felt that they may do harm to themselves or others. Since there are no facilities for such close observation on medical or surgical wards, they are transferred to the closed wards of the Psychopathic Department and their treatment continued there. Therefore, the senile patients are classed together and treated as a separate group in this study, in order to make the remainder of the cases assume proper proportion.

These patients are studied, treated and finally disposed of, in several ways. They are treated if there is any specific therapy and if it is felt that they can be improved in a relatively short time. This includes electroshock therapy and malaria fever therapy. They may be transferred to private institutions, nursing homes or other appropriate facilities. Finally they may be committed to a state institution if considered chronically ill. The turnover of patients is relatively and necessarily rapid, so that, as indicated, this survey deals with mortalities on an acute psychopathic department.

Statistical Data. In the period of 12 months being considered, there was a total of 3374 admissions. Of these, 827 fell in the senile group. The total number of deaths was 332, with 231 of these admitted primarily because of senile changes and death resulting from the usual geriatric causes, predominantly pneumonia. The mortality data are summarized in Table 1. Of particular interest to us are the patients included in the "Remainder" group.

Those in the "Remainder" group who died included 70 men, 31 women; 77 white, 23 colored, 1 yellow. Of the 101 cases, 59 were autopsied, including 20 which were coroner's cases (those dying within 24 hours after admission or in consequence of suspicious circumstances). The hospital stay averaged 13 days, with the range from less than 1 hour to 73 days. Age ranged from 23 years (a deteriorated epileptic) to 80 years (hypertensive cardiovascular disease), with an average of 53 years.

Table 2 lists the primary diagnoses and number of deaths in each group. The larger groups are discussed below.

Under the diagnosis of cardiovascular disease are listed all cases whose psychosis appeared to be due primarily to a circulatory disturbance and who subsequently died of it. It includes such cases as hypertensive encephalopathy with or without uremia, hypertension with cerebral accident, coronary occlusion, and cerebral embolus. (The senile group mentioned above included those cases of senile psy-

chosis, and psychosis with cerebral arteriosclerosis.) Of the total 33 cases, the primary psychotic manifestation of 13 (39.7%) was marked confusion or coma, 12 (36.3%) were agitated, and 8 (24%) were depressed, 7 of these having attempted suicide.

the use of intravenous vitamin therapy. Three cases (21%) had severe head injuries, 2 of these had subarachnoid bleeding and 1 of the latter showed laceration of brain at post. One case at autopsy showed generalized hypoplasia of all organs, including the circle of Willis;

TABLE 1.—DATA ON MORTALITY AMONG 1 YEARS ADMISSIONS TO PSYCHOPATHIC DEPARTMENT

	No. cases admitted	Deaths	Mortality (%)
Total	3374	332	10.0
Seniles	827	231	28.3
Remainder	2547	101	4.0

TABLE 2.—CAUSES OF DEATH AMONG PSYCHOPATHIC ADMISSIONS OTHER THAN SENILE PATIENTS

	No. of deaths and % (101 cases)
Cardiovascular disease	33
Alcoholism	14
General paresis	13
"Agitation"	10
Tuberculosis	5
Neoplasm elsewhere with cerebral metastases	5
Brain tumor	3
Epilepsy	3
Bromism	3
Tuberculous meningitis	2
Suicide	2
Morphinism	1
Gangrenous cystitis	1
Digitalis toxicity	1
Marie-Strümpell disease	1
Malnutrition	1
Pachymeningitis hemorrhagica	1
Ruptured miliary aneurysm	1
Alzheimer's disease	1
Total	101

TABLE 3.—DATA ON THE CHIEF CAUSES OF DEATH AMONG NON-SENILE PSYCHOPATHIC ADMISSIONS

	No. deaths	No. admissions	Mortality (%)
Cardiovascular disease	33	273	12.1
Alcoholism	14	479	2.9
General paresis	13	235	5.5
Epilepsy	3	83	3.6
Bromism	3	10	30.0

Table 3 shows the chief causes of death among the non-senile patients.

The alcoholics are grouped together and include all cases whose admission to the hospital was primarily because of some form of alcoholism. These include 7 chronic alcoholics, 5 cases of delirium tremens, and 2 of alcoholic hallucinosis.. The largest number, 8 patients (57%), succumbed to pneumonia. This group is undoubtedly smaller than formerly because of the advent of the sulfa drugs and

1 had had a cerebrovascular accident, and 1 who had been drinking a combination of alcohol and ether showed acute and chronic hepatosis with hepatic insufficiency. There was 1 patient with Korsakoff's syndrome due to alcohol, who went downhill rapidly despite therapy and died, but no autopsy was performed.

In the group with general paresis, all 13 had positive spinal fluid findings for syphilis. Seven were old known cases of general paresis, deteriorated on admis-

sion; 3 were quite agitated when they first came to the hospital and became rapidly worse; 1 developed a sudden elevation of temperature (not receiving fever therapy) and died. The postmortem examination showed syphilitic aortitis and pulmonary emboli. One patient was treated with deep Roentgen ray therapy according to the method of F. Bering, and 11 days after the last treatment developed convulsive seizures and died. No patient of this group was on malaria fever therapy at the time of death.

The 10 cases listed as "agitation" are grouped together because all were admitted to the hospital in agitated states, all were studied as thoroughly as possible but no definite medical diagnosis could be established, and all died without obvious cause; 5 were examined postmortem and none showed anything except terminal bronchopneumonia and chronic passive congestion of other organs. One was a coroner's case because he died in less than 24 hours after admission into the hospital. There were 4 women and 6 men, ranging in age from 25 to 60 years, with an average of 44. The stay in the hospital varied from a few hours to 56 days. There were 2 Negro and 8 white patients. On admission to the hospital the provisional diagnosis was schizophrenia for 5, agitated depression for 3, reactive depression for 1, and toxic psychosis for 1.

Two of the "agitated" patients died rather acutely. The first was a 25 year old Negro male who became irrational at work, heard voices and was very agitated and noisy. On admission to the hospital he was restless, confused and very difficult to control. Physical examination was essentially normal. A mild sedative was administered but the agitation continued and he died approximately 6 hours after admission. A postmortem examination by the coroner revealed no specific cause of death. The second was a 49 year old white male who also became agitated while at work. This continued until he was hospitalized. On the ward he was extremely restless and irrational. Past history was non-contributory. Physical examination showed a temperature of 105° F., pulse 125, respirations 36. The leukocyte count was 28,000, with 81% neutrophils and 19% lymphocytes. The agitation and restlessness continued and the patient died 2 days after admission. A postmortem was done and all organs were essentially normal, including the brain which showed only "acute and chronic passive congestion."

In the remaining 8 "agitated" cases, death occurred in from 12 to 56 days. The youngest of these was a 27 year old white male who had been acting strangely for 2 to 3 weeks prior to hospitalization. He had been going about ringing doorbells, had been unable to sleep and was continually masturbating. He was markedly hyperactive and agitated on admission. Physical examination was essentially normal. Temperature on admission was 99° F., then fluctuated irregularly as high as 106°. The pulse was 110 on admission and rose at times to 130. Respirations were 25 on admission and fluctuated to 45. The leukocytes numbered 14,900, with neutrophils 94% and lymphocytes 6%. Blood urea nitrogen was 27 mg. per 100 cc. The patient's course in the hospital was progressively downhill and he died on the 12th day. Postmortem examination showed only "chronic passive congestion," including the brain.

A second "agitated" patient who lived for 12 days was a 38 year old Negress who was admitted to the Tuberculosis Department because she appeared toxic and had a fever ranging from 102° to 104° F. She became hallucinated, appearing like a case of delirium tremens, expressed many bizarre complaints, and had to be transferred to the closed wards. Physical examination was essentially negative and the results of all laboratory studies, including chest Roentgen rays, were normal. This activity and agitation continued and the patient died on the 12th day. An autopsy was not obtained.

A 43 year old white married male was admitted to the hospital because he had

begun to worry about an affair he was having with a girl he had met in church. He began to hallucinate, was taken to his doctor and became upset and struck him. Upon admission to the hospital he was actively hallucinating and expressed many delusional ideas. He was quite agitated and restless. Physical examination was essentially negative. Sedatives were given and included intravenous sodium amytal (the latter for both sedation and abreaction without obvious effect). The increased activity persisted. The temperature rose to 103° F., pulse and respirations increased. All laboratory studies including agglutination tests for typhoid and the paratyphoid groups were negative and the patient died on the 13th day. No autopsy was obtained.

The 3 cases of "agitated depression" ran a similar course to those described above. Two of these were given electroshock therapy. One of these 2 had been given a complete course and was sent home, but returned quite agitated and disoriented, remained that way for 10 days and died. Postmortem examination showed only a "terminal bronchopneumonia." The other was given 11 electroshocks, but agitation and depression persisted. Three days after the last treatment, and while still agitated, the patient developed Cheyne-Stokes respirations, became cyanotic and died despite treatment. Unfortunately no autopsy was obtained.

The remaining 2 "agitated" patients were females, 1 of whom appeared schizophrenic on admission, the other suggesting a reactive depression. The former had a history of previous mental breakdown 25 years before the present admission. This time she was excited, agitated and had shown violent behavior since the birth of a child 4 months ago. She had a persistent fever but all studies, including agglutination tests, were negative. Sulfa drugs were tried empirically but the agitation and restlessness persisted and patient died. The postmortem examination showed only bronchopneumonia.

The last case of this group was a 50 year old white female who became jittery and worried about her alcoholic husband. She became negativistic, would not eat and appeared malnourished on admission. She was quite agitated, required restraint and tube feeding. She was extremely uncooperative, became mute and died on the 21st day.

In the group with tuberculosis, 2 attempted suicide unsuccessfully and were admitted to the wards as cases of depression. One patient was admitted because of agitation; 1 was comatose on admission and 1 case, brought to the hospital as mild senile psychosis, showed tuberculous pneumonia at necropsy.

In the 5 patients with metastatic brain tumor the primary growth was bronchogenic carcinoma in 2, and carcinoma of stomach, larynx and cervix respectively in the other 3. Four of the 5 were admitted because of agitation, 1 was confused and showed marked organic deterioration. All 5 cases were examined at autopsy.

Unfortunately, of the 3 patients believed to have primary brain tumor, only 1 came to necropsy. The tumor proved to be an astroblastoma of splenium corpus callosum. The other 2 patients had definite clinical findings pointing to intracranial lesions, cerebellar in 1, and in the right temporal lobe in the other.

Of the 3 epileptics, 1 was a 23 year old Italian woman, markedly deteriorated, agitated and confused, who died 2 days after admission. The second was a 61 year old woman who had been a known epileptic for 25 years, was admitted to another hospital as suspected intestinal obstruction, became overactive, irrational and disoriented, and died 7 days after admission. The last case, a known epileptic, was a 28 year old white man markedly agitated and confused on admission, with a rectal temperature of 107° F. (found to have a subarachnoid hemorrhage of unknown etiology), and died on the 4th day (no autopsy).

The 3 cases of bromism had blood bromides (on admission) of 420, 340 and 265 mg. per 100 cc. respectively. Two were

known to be heavy alcoholics. All 3 were comatose on admission, 2 were started on sodium chloride, the other died before treatment could be instituted, all dying within 1 week of admission to the hospital.

The 2 patients with tuberculous meningitis were both stuporous on admission and died 5 days later. The 2 cases of successful suicides were both involutional melancholia. The remainder of the cases are as listed.

Of the so-called purely functional psychoses, there were no deaths among the clear-cut schizophrenics (although some of the "agitation" group may fall in that class), none was a proven or known manic-depressive psychosis, and there were 2 successful suicides among the involutional melancholics.

Summary. 1. A survey of the causes and incidence of death in an acute psychopathic department was made. Of 3374 patients admitted in 1 year, 332 died. Senile patients numbered 827, of whom 231 died. Of the 2547 non-senile patients, 101 died. The causes of death in the latter group are analyzed.

2. The commonest cause of death was cardiovascular disease.

3. Alcoholism and general paresis were about equal as the next commonest causes of death.

4. Ten per cent died of "agitation" of unknown etiology.

5. Tuberculosis and neoplasm (both primary in the brain and metastatic) were next in frequency.

We wish to acknowledge our indebtedness to the Pathology Dept., especially Dr, Helena Riggs and Dr. William Ehrich.

THE EFFECT OF AMINOPHYLLINE ON THE PROTHROMBIN TIME IN MAN

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In 1944, Link and his co-workers published a series of observations on the action of certain xanthines on the prothrombin time of several experimental animals.[2,3,4] They were able to demonstrate that large single doses of caffeine, theophylline, theobromine, aminophylline, and other xanthines, when given orally to the dog, rabbit or rat induced a state of hyperprothrombinemia which was readily detectable in diluted (12.5%) plasma. When these animals were given 3,3′-methylenebis - (4 - hydroxy - coumarin) with the methylxanthines, the expected hypoprothrombinemia was partially neutralized. Relatively large therapeutic doses of aminophylline (12, 24, 36 mg./kg. by mouth daily) produced a hyperprothrombinemic effect in dogs detectable in 2 to 5 days, and maintained for periods as long as 30 days. The authors suggested that, "Since our results . . . indicate that the methylxanthines not only render the blood hypercoagulable, but also counteract such a potent hypothrombinemic agent as 3,3′-methylenebis-(4-hydroxy-coumarin), it is conceivable that their use in man might augment the tendency for thrombus formation."[2] It was to determine the effect of therapeutic doses of aminophylline on the prothrombin time of man that this study was undertaken.

Method. Many workers have advocated the use of diluted (12.5%) plasma in order to detect small changes in prothrombin times.[2,3,4,6,7,8,9] The determinations of prothrombin time were done by the Quick method,[5] as standardized by Aggeler, *et al.*[1]

All experiments were performed on fasting blood, and were completed within 2 to 6 hours after the specimens were drawn. The subjects were young, adult, male patients with mild bronchial asthma, in a Naval Hospital. They were under no other drug therapy at the time of the study. Five cc. of blood were mixed with the dry oxalate mixture of Heller and Paul (4 mg. potassium oxalate and 6 mg. ammonium oxalate). After centrifugalization the plasma was diluted to 12.5% with 0.85% sodium chloride. In all experiments a single specimen of dehydrated human brain, prepared by acetone extraction and stored in an evacuated desiccator, was used.* Under these conditions, 0.005 M. calcium chloride solution was found to produce optimal results. All determinations were made in triplicate at 37° C. and the results averaged.

Results. 1. *Normals.* (*a*) Prothrombin times were determined on 10 normal individuals, using 12.5% plasma. In this series, the mean was 24.5 seconds, the range 22.7 to 26.8 seconds, and the standard deviation plus or minus 1.4 seconds. These values are comparable to those found by other workers using this method.[5]

(*b*) Prothrombin times were determined on 10 separate specimens of blood from a single individual. In this series the mean was 24 seconds, the range 19.8 to 25.8 seconds, and the standard deviation plus or minus 1.7 seconds. Using 2.5 as the level of significance, it can be shown that a difference of plus or minus 4.3 seconds (from the mean) is required for the variation to be significant. This means that a change in prothrombin time in any given series on 1 individual would have to be

* This material was supplied by Dr. Paul M. Aggeler, to whom we wish to express our thanks.

greater than 4.3 seconds in order to be certain that the variation was not due to chance.

2. *Effect of Small Oral Doses of Aminophylline.* A group of 5 patients were given aminophylline, 0.1 gm. orally 3 times a day for 7 days. Prothrombin determinations before, during, and after therapy showed no significant change in the prothrombin time (Table 1). None of the patients developed toxic symptoms.

Table 1.—Prothrombin Time in Seconds of 12.5% Plasma Following Aminophylline in Oral Dosage of 0.1 Gm. 3 Times Daily for 7 Days

Patient:	W. K. A.	K. W. B.	J. S. B.	J. A. C.	T. W. C.
Before aminophylline	26.8	23.3	22.2	23.2	22.0
Before aminophylline	26.2	24.0	22.5	24.8	23.5
On 5th day of therapy	23.3	24.5	24.7	22.8	27.3
1 day after discontinuance of therapy	24.3	26.0	23.8	25.2	27.7

Table 2.—Prothrombin Time in Seconds of 12.5% Plasma Following Aminophylline in Oral Dosage of 0.5 Gm. 3 Times Daily for 2 Days

Patient:	M. K. A.	H. J.	E. H. P.	H. L. G.*	J. M. C.†
Before aminophylline	24.3	25.5	25.3	..	27.7
Before aminophylline	24.0	25.2	24.0	24.5	28.7
After 1 day of therapy	28.3	26.8	26.8	25.5	27.0
After 2 days of therapy	22.5	25.5	24.7	21.3	
3 days after discontinuance of therapy	23.3	24.5	24.0	24.7	28.3

* This patient received aminophylline, 0.5 gm. intravenously, on 1st day of therapy in addition to oral dose.

† This patient received 0.5 gm. aminophylline 3 times a day for 1 day only.

Table 3.—Prothrombin Time in Seconds of 12.5% Plasma Following Intravenous Administration of 0.5 Gm. of Aminophylline

Patient:	M. K. A.	H. J.	E. H. P.
Before aminophylline	22.0	23.8	22.8
Before aminophylline	24.0	22.7	24.3
3 hours after administration	24.3	24.7	22.4
24 hours after administration	24.3	25.5	25.3
72 hours after administration	24.0	25.2	24.0

3. *Effect of Large Oral Doses of Aminophylline.* A group of 4 patients were given aminophylline, 0.5 gm. orally 3 times a day for 2 days. Prothrombin determinations before, during and after therapy showed no significant change in the prothrombin time (Table 2). All of the patients experienced minor toxic symptoms of anorexia, slight nausea, and nervousness.

4. *Effect of a Single Intravenous Dose of Aminophylline.* Three patients were given 0.5 gm. aminophylline intravenously and prothrombin times were determined before, during and after therapy. Again, no significant change was observed (Table 3).

Comment. It has been shown that, in man, hyperprothrombinemia can be detected using 12.5% plasma.[6,7,8,9] In this small series, no hyperprothrombinemia could be demonstrated following administration of aminophylline. It would seem, then, that the fear that aminophylline may produce hyperprothrombinemia (and an increased tendency toward thrombus formation) is unwarranted, and does not constitute a contraindication to the therapeutic use of the drug.

Summary and Conclusion. Aminophylline administered orally and intravenously in full dosage to a small series of human subjects produced no significant change in the prothrombin time.

The therapeutic use of the drug therefore probably does not involve any increased threat of intravascular clotting.

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PROGRESS
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UNDER THE CHARGE OF
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TUMORS OF THE SKIN

PART II. A REVIEW OF RECENT LITERATURE*

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Epithelioma (Cutaneous Carcinoma). For ordinary considerations cutaneous epitheliomas are divided into 2 groups, those of basal cell and prickle or squamous cell or epidermoid carcinoma. This distinction might appear of little significance but, as indicated above, the differences in course, location, treatability, metastasis, etc., make this distinction of practical if not theoretical, importance.

Basal cell epitheliomas vary in size from small to large, are chronic, with a slowly growing superficial to deep nodule or ulcer and a rolled pearly, telangiectatic border, the center of which is usually covered with a crust, removal of which causes bleeding. This type of lesion occurs predominantly on the anterior portion of the face and forehead (Glasunow;[100] McFarland, Ciccone and Gelehrter;[182] Schrek;[262] Sutton[287c]), but it may occur anywhere on the body. Histologically, there is a varying arrangement of strands, like a lattice network, a glandular arrangement, or a solid growth of basal cells arising from the basal cells of the epidermis, rarely from the basal cells of the dermal appendages. Montgomery[193e] has made an extensive study of the histogenesis of these tumors and his classification of epithelioma presumably of basal cell origin is worth serious consideration.[193e]

Basal cell epitheliomas may be benign, but in time local destruction may occur involving both cartilage and bone. They do not metastasize and those which seem to have metastasized will turn out on examination to be basal squamous or squamous cell epitheliomas (Montgomery[193a,e]). Pigmented basal cell cancers may occur. The pigment (melanin) is deposited in and between the cells of the tumor. Examples of the pigmented basal cell epithelioma have been reported by Eller and Anderson,[83] Becker,[23a] Montgomery,[193c] and by Quiroga and Helman.[243] These latter authors believe that pigmented lesions are not rare. On superficial examination, these pigmented basal cell epitheliomas may resemble pigmented nevi or melanomas; but they are much firmer and more indurated than pigmented nevi and of perhaps a more brownish rather than bluish color more characteristic of melano-epithelioma. They also do not show extension along the lym-

* The first part of this review appeared in the April issue.

phatics. On the other hand, Nisbet[210] has reported another case of the type originally described by Nomland[212b] of multiple basal cell epitheliomas originating from congenital pigmented basal cell nevi. These cases had the gross clinical appearances of pigmented nevi. Angiomatous forms of basal cell epithelioma have been reported by Lamb, Geschickter and Lain.[148] Basal cell epitheliomas may also resemble other dermatoses such as, for example, senile sebaceous adenomas, a benign lesion also named by Nomland.[212a] (See above.)

Montgomery[193f] states that about 20% of neoplasms diagnosed clinically as basal cell epitheliomas are in reality transitions between basal and prickle cell lesions, the so-called basal squamous cell epithelioma. While there is no clinical difference between basal cell and the transitional form, histopathologically they are characterized by a definite picture of partial pearl formation, with brightly staining colloidal-like centers, light-staining intermediary and prickle cells and darker staining basal cells at the periphery. They tend to infiltrate the tissue in narrow strands, both going down and reaching out at the margins of the lesions. This fact indicates the need for wider excision than for basal cell epitheliomas.

Treatment of basal cell epitheliomas is by excision, electrodestruction or radiotherapy. The type of therapy depends on the size and location of the lesion. Warren and Lulenski[320] found basal cell epitheliomas to have a less formidable prognosis than have epidermoid carcinomas from the standpoint of mortality, but they have a very little better outlook as far as 5 year cures are concerned. This is a point that should be stressed, since the clinician usually regards basal cell cancer as a relatively benign lesion and one of small importance. A visit to the cancer wards of any large city general hospital will soon dispel any doubt about the disabling propensities of this type of tumor.

Prickle cell carcinoma usually presents a wider and more indurated border than basal-cell epitheliomas. Senile keratoses are frequently forerunners of this type of lesion. They are most apt to occur on the exposed parts of the body. They may attain large size and be destructive. Carcinoma of the mucous membrane is always of this variety. They may resemble other disorders, especially gumma, if situated on the lip or tongue. Broders, as previously stated, classifies these tumors in 4 grades depending on the amount of differentiation of the individual cell, mitosis and pearl formation. Squamous cell carcinoma has a decided tendency to metastasize, especially Grades 3 and 4 of Broders. Treatment should be radical and the type will depend on the situation and type of lesion. End-results are worse than in basal cell epithelioma, which has the advantage of slow development, non-metastasis and occurring on an accessible situation. Squamous cell cancer is thoroughly discussed in the surgical and radiologic literature.

Calcifying Epithelioma (Malherbe's Epithelioma). This type of tumor had received little attention in the American literature until Ch'in's[54] article in 1933 and Sutton and Sutton's[256a] report of a case in 1935. The distinguishing features of this tumor as outlined by the Suttons are as follows:

"(*a*) The spherical shape. (*b*) The size generally of from 1 to 3 cm. (*c*) The location under the derma, fixed to the skin above and freely movable over the deeper tissues. (*d*) The hardness, which may be almost bony. (*e*) The occurrence (in order of frequency) on the head, arms, forearms and back, then elsewhere. (*f*) The occurrence in persons of any age, but often in youth or in early adult life. (*g*) The spicular, gritty surface of the gross section. (*h*) The component bands of epithelium, which hornify, calcify and become engulfed by giant cells. (*i*) The encapsulation and continuity with the capsule of a dense fibrous stroma remarkable for the giant cells in its structure. (*j*) Its behavior as a benign

neoplasm or local growth. (*k*) Its amenability to local excision with permanent cure."

Highman and Ogden[119] (1944) believe the most characteristic feature to be eosinophilic degeneration of the epithelium which they think is a form of dyskeratosis.

Malherbe and Chenantis,[175] in 1880, were the first to describe this type of tumor as calcifying epithelioma of sebaceous glands. Since then reports have appeared, especially in the French and German literature. Ch'in, in 1933, reported on 10 tumors with this diagnosis gathered from over 22,000 surgical specimens covering a 15 year period. From a study of the literature he collected 116 additional cases. Coté[63] reported 12 cases in 1936. Highman and Ogden[119] reported on 1 probable and 11 definite tumors of this type gathered from a series of 24,185 surgical specimens received over a period of 15 years.

This tumor may occur at any age. In Highman and Ogden's series, in which most of the diagnoses were on a clinical basis, the age range was between 17 months and 66 years. In a recent series of 13 cases reported by Muehlon, which clinically were thought to be mostly dermoids or atheromatous change, the lesions first appeared in 8 persons less than 20 years of age, in 4 persons 20 to 30 years old and in 1 at the age of 65 years. Highman and Ogden found the cases to occur in 4 females and 8 males, a ratio of 1 to 2. Muehlon, however, found 9 in females and 4 in males.

The origin of the tumors is not clear. According to Highman and Ogden they have been variously regarded as endothelioma, atheroma, basal cell carcinoma, a derivative of an epithelial rest, a result of traumatic epithelial inclusions, cholesterotoma and dermoid and epidermoid cyst. Malherbe suggested that the lesion results from abnormal proliferation of the lining wall of a sebaceous cyst. Kaufmann[139] stated that the origin may be in preformed glands as well as in deep-lying (dystopic) epithelial cells, probably misplaced anlage material. Coté expressed the belief that it was a lesion sui generis possibly derived from the anlage of a sebaceous gland in which the final growth occupies an intermediate position between epidermoid cyst and basal cell epithelioma. Muehlon believes these lesions are hamartomas, the peculiar feature of which is that the aberrant basal cells are potentially destined to eventual spontaneous necrosis. Highman and Ogden suggest that these tumors may have an origin from or similar to that of hair follicles.

Multiple Superficial Epitheliomatosis. Much of the literature on this subject has been recently reviewed by Weisman and Medalia.[330] Multiple superficial epitheliomatosis, as distinct from morphea-like and superficial types of arsenical epitheliomas, was first clearly described by Graham Little[162] in 1923 under the name of "erythematoid benign epithelioma." Wise[338] claimed that prior to this time it was called multiple benign superficial epithelioma. In recent years there has been considerable confusion as to what constitutes this process clinically and histologically. Savatard[259a] concluded from a survey of the literature of a 60 year period that, because of the protean clinical and histologic manifestations, variants of this dermatosis have been described as separate entities. He maintained that mammary and extramammary Paget's disease of the skin, erythroplasia of Queyrat, and Bowen's precancerous dermatosis were different forms of the same disease. He found in his experience that they all resembled a psoriatic plaque and he accordingly proposed the name, "psoriasiform carcinoma of the skin" for them. This is not in keeping with the experience of Montgomery[193b] and others, which leads to a distinction between superficial epitheliomatosis and the aforementioned states. Bowen's disease is, according to Montgomery, in reality a squamous cell epithelioma *in situ*. Dörffel who found 18 cases among 200 epithelial

skin tumors studied histologically between 1925 and 1935 (University of Königsberg) felt that there were few characteristic features in these lesions. He differentiated them from lesions of eczema, psoriasis, lichen planus, syphilis, lupus erythematosus, Bowen's disease and Paget's extrammary dyskeratosis. Biopsy is necessary to establish the diagnosis. The cause of multiple superficial epitheliomatosis is unknown. Ingestion of arsenic was frequently suggested to explain the lesions (Tauber and Goldman;[293] Hopkins and Van Studdiford;[125] Ayres;[16] Anderson;[11b] Wright and Friedman[341]). It is more frequent in women than in men (14 to 4, Dörffel; Madsen[174]). Madsen believes the lesions are unicentric in origin.

The lesions may be dry or eczematoid in type. They first appear on the trunk as erythematous, smooth, flat, irregular, shiny macules and papules, which gradually enlarge and coalesce to form plaques 2 or 3 cm. or more in diameter. A fully developed case has multiple reddish to violet discoid patches of variable size up to 20 cm. in diameter. Many of the patches are smooth and not infiltrated. A certain amount of scaling, oozing and crusting may be a feature. There is a characteristic fine thread-like, somewhat elevated border surrounding the lesions. There may be central healing consisting of a white atrophic surface with some telangiectasia in some of the long-standing lesions. They may persist with little change for as long as 40 years.

Madsen[174] in his monograph based on his own 10 cases and the literature adds new features, such as melanin in the plaques and the occurrence in younger persons. He believes the pigment is the result of inflammatory reaction in response to tumor. The lesions are single in 42% of the cases; they may in rare instances exceed 200 to 400 (Pautrier and Achambault; van der Meiren). They may occur anywhere except on the palms, soles, fingers, toes and genitalia. The dorsum of the hand is a rarely affected site. The course is benign, metastases are rare, though local recurrences are frequent. We have seen recurrences at the margins of treated lesions even in some which have sustained an irradiation reaction (atrophy and telangiectasia).

Metastatic Cutaneous Malignancy. Cutaneous carcinoma may result from carcinoma situated anywhere in the body, and may occur at any age—even in the newborn[25]—but usually late in life. Such involvement may arise: (1) by extension by direct invasion from adjacent tumors; (2) by extension through the lymphatics (Sampson-Handley's "permeation"); (3) dissemination through lymphatics with or without involvement of the lymph nodes between the primary growth and the metastatic lesion; (4) the dissemination through the blood stream, as occurs in many cases of cutaneous metastasis. Only the last two are metastases in the strict sense of the word. The incidence of cutaneous metastasis of malignant disease is not high. In a study devoted to this subject Olive Gates[96] found metastases of the skin in 93 (0.1%) of 82,298 specimens; 29 (0.04%) from 80,000 surgical specimens, and 64 (2.7%) from autopsy specimens of 2298 malignant tumors. Gates regards the autopsy series as probably the more representative figure. Her figures are higher than those in the literature on the frequency of secondary skin tumors (0.01 to 0.7% for all types of cases malignant and nonmalignant). Of 2031 carcinomas in the autopsy series, 43 (2%) had skin metastasis. In the group from the literature the number of skin metastases from mesenchymal and epithelial tumors is practically the same, 176 sarcomas against 173 cases of carcinoma. Carcinoma of the breast is the most important primary tumor site in this respect, producing as many secondary skin tumors as all other types together. Among 58 metastatic tumors, 25 originated in the breast; however, collected cases from the literature showed only 8 out of 173 metastatic carcinomas primary in the breast. This may be due partly to the fact that skin

tumors from breast carcinoma are so common as to excite little interest and partly to the common assumption that they result from lymphatic permeation and are not true metastases. The remaining 24 cases in Gates' series arose from 14 different organs: 4 from the lung; 3 each from the uterus and kidney; 2 each from the stomach, rectum and pancreas; 1 each from the liver, adrenal, thyroid, tonsil, jaw, urethra, prostate and penis. From the literature, carcinoma of the stomach (54 cases) produced the majority of secondary skin tumors. After the stomach the order of frequency is: uterus, 17 cases; lung, 15; large intestines, 13; kidney and ovary, 10 each; esophagus, 5; liver, 4; urinary bladder, 3; tonsil, pharynx, trachea, adrenal, thyroid, 2 each; nose, larynx, parotid, tongue, penis and gall bladder, 1 each. In both series excepting breast and stomach, carcinoma of lung, uterus and kidney are the most important sources of skin metastases, the incidence varying from 5 to 9%. If carcinoma of the breast is withdrawn from both series, the incidence for different sources of epithelial skin metastases is practically unchanged for the literature group, but is considerably increased for carcinomas of Gates' series. The stomach has long been considered the most important source of skin metastasis, but the statistics from the literature are contradictory on this point, and do not altogether substantiate this assumption. From Gates' analysis it appears obvious that carcinoma metastatic in the skin is frequently not recognized. The importance of these metastatic lesions is that they are often the first evidence of the existence of malignancy and also of metastasis. These cutaneous metastases are not necessarily immediate precursors of death. They are of limited prognostic value, since the behavior of the skin tumors does not necessarily indicate rate of growth of the primary tumor. The gross appearance of skin metastases is not distinctive. They have a predilection for certain sites, especially the chest, in the axilla, on the abdomen and in the perigenital region. In some cases the secondary growth may overlay the primary tumor. The scalp is rarely affected by metastasis; when found it must be distinguished from turban tumors and carcinomas of various dermal appendages (Montgomery and Kierland;[199] Ronchese[252b]). Ovarian carcinoma with metastases to the skin has rarely been reported. Urbach, Waldow and Stamm,[311] in an interesting case report of diffuse metastatic lesions from an ovarian carcinoma, review the literature and note only 8 cases besides their own, the first in the American literature. This case is especially interesting because of erysipelas-like features resembling the condition known as "erysipelas carcinomatosum" (Lee and Tannenbaum;[152] Rasch;[246] Pfahler and Case[229]). Unfortunately the authors did not mention Gates' paper in which 10 cases of ovarian carcinoma with cutaneous metastases were gathered from the literature, although she had no personal cases. Since Gates does not detail the source of her cases from the literature, Urbach and his associates' case still appears to be the first in the American literature. Nicholas[209] reported a case of acanthosis nigricans in which deep cutaneous and subcutaneous metastases from a retroperitoneal lymphosarcoma were observed histologically. This case suggested the advisability of examination of the deepest parts of the corium and subcutaneous fat in future histologic studies of acanthosis nigricans. Nödl has recently reported skin metastases of a malignant hypernephroid tumor.[211b]

In Gates' group of 442 cases of cutaneous metastases, there were 200 mesenchymal tumors. Lymphomas and leukemias make up 94% of the mesenchymal tumors and 43% of the entire group. These mesenchymal tumors made up 23% of her autopsy group. Of these the lymphomas and leukemias are the most important groups, secondary skin tumors being present in 8 (9%) of 85 lymphoma autopsies and in 31 (6%) of 50 leukemia

autopsies. A little over one-half of the lymphomas in the series of leukemia cutis were from autopsies. This is explained on the basis that in lymphoma cutis the primary disease is less obvious than in leukemia and diagnosis frequently depends on biopsy. The lymphoma-leukemia group was responsible for most of the widespread cutaneous metastases (53 of 69 instances were in this group).

Cutaneous Carcinoma Arising From Various Cutaneous Disorders. A number of cutaneous diseases have been secondarily affected by carcinoma. Among them are xeroderma pigmentosum, rhinophyma (Novy[214]); Darier's disease (Carache[47]); sebaceous cyst (Stone and Abbey[279]); psoriasis (arsenic?) (Wright and Friedman[342]); lupus vulgaris (0.5 to 1% of cases) (Ormsby and Montgomery[216]); acrodermatitis chronica atrophicans (Pack and Wuester[223]); radiodermatitis; osteomyelitic cavity or sinus (Steward, Obermayer and Woolhandler;[276] Bereston and Ney[28]); lupus erythematosus, granuloma inguinale and lymphogranuloma venereum. One must be careful to be certain in some of these supposed carcinomatous complications that he is not dealing with pseudo-epitheliomatous change. Only lupus erythematosus and lymphogranuloma venereum will be detailed here. The mechanism of the carcinomatous change is not clearly understood in most of the disorders listed. Trauma, arsenic, irradiation (sun, Roentgen ray) are among the proposed explanations.

(*a*) *Epithelioma as a Complication of Lupus Erythematosus.* In reviewing this complication of lupus erythematosus, Ambrosetti[8] stated that epithelioma is not exceptional in lupus erythematosus, but is not as frequent as is the case of lupus vulgaris. Dicke[72] collected 50 cases, 3 personal; Veiel[312] collected 90 cases; Tischnenko[299] collected 91 cases (1 basal cell), remainder were prickle cell carcinoma. These cases are supposed to occur most often after prolonged irritation (pyrogallic acid) or injudicious amounts of radiotherapy.

Uhlmann and Schambye[308] believe that cancer was not rare in this dermatosis, but denied that Roentgen rays facilitated its development. Louchtchitzky[165] observed 400 patients of whom 15% (60) were irradiated with Roentgen rays, 6 (4 women and 2 men) presented epitheliomas (10%). These appeared 6 months to 7 years after the application of the roentgenotherapy. There were no cases of cancer among those who did not receive Roentgen irradiation. He believed that these patients had hypersensitivity to Roentgen rays and considered it a dangerous type of treatment which should be avoided in the treatment of lupus erythematosus. Pautrier[225] cited 2 cases of prickle cell cancer of the lips. Le Coulant[151] presented a case of precocious spirocellular epithelioma of grave prognosis in a patient who had had no previous radiotherapy. Kogoj[145] encountered only 3 cases of epithelioma among 385 patients with lupus erythematosus. In 315 patients of Puente[238] there were only 2 examples of epithelioma; 1 following Roentgen therapy, the other occurring without previous Roentgen irritation.

(*b*) *Malignancy and Lymphogranuloma Venereum.* Deibert and Greenblatt[71] believe that genital malignancy may be coexistent with, simulated by, or a direct sequel of one of the venereal diseases. They believe the association of the malignancy and venereal disease is too frequent to be coincidental. Etiologic relation has been suspected by a number of authors as Pund, Greenblatt and Huie;[239] Cardwell and Pund;[48] Liccione;[159] David and Loring;[69] Lisa;[160] Reeves;[248] Greenblatt;[109] Smith;[270] Taussig.[295c] Lately Guzman[115] reported vulvar involvement of lymphogranuloma venereum and carcinoma. Similar associations were reported by Cardwell and Pund; Pund, Greenblatt and Huie and Deibert and Greenblatt. Binkley and Derrick[33] reviewed the literature on the association of squamous cancer with anal manifestations of lymphogranuloma venereum. Among 87 cases of squamous cancer of the anus and rectum at the

Memorial Hospital in New York, study revealed 8 positive and 11 negative Frei tests among 19 tested. The remainder of the cases were treated prior to the routine employment of the Frei test. It is necessary to point out that the Frei test, made with all types of antigens, cannot, in the Reviewer's opinion, be relied upon implicitly as an indication of the existence of lymphogranuloma venereum.

Malignant Melanoma. Without entering into the long-standing controversy as to the epidermal *versus* mesodermal region of these tumors, we shall discuss them under the non-committal name of malignant melanoma, as proposed by Becker,[23b] but with the conviction based on the best American dermatologic authority that they are really probably epidermal origin (melano-epithelioma). Among the recent papers on this subject are the general discussion of Becker (1936); Butterworth and Klauder on malignant melanomas arising from moles;[45] Netherton[206] on cutaneous and nervous system involvement; Reese[247a] on precancerous melanosis and diffuse malignant melanoma of the conjunctiva and his later study;[247b] Dixon;[74] Daland and Holmes;[67] Pack and Adair[221] on subungual melanoma; Moersch, Love and Kernohan;[191] Taussig and Torrey;[295d] Sweet and Connerty;[288] Howes and Birnkrant;[128] Tod;[300] Driver and MacVicar.[77a]

Malignant melanoma is essentially a disease of the white race. It occurs more frequently in males. These lesions may occur at various ages, but the average is around 50 years. For example, Howes and Birnkrant (1943) found an average age of 52.4 years (youngest 22 years) among their 32 patients. Taussig and Torrey found an age range of 5 to 86 years, with an average of 48.7 years. Sweet and Connerty presented a case with antenatal metastasis. The process usually begins as a solitary blue black or steel blue flat or elevated nodule, plaque or tumor of several millimeters to several centimeters in diameter. Occasionally the color may be a lighter brown, especially when a pigmented nevus undergoes malignant change. These lesions occur on any part of the body, but most frequently on the extremities and exposed parts (Howes and Birnkrant; Butterworth and Klauder). Trauma may have a possible influence on their frequent occurrence in exposed locations (implantation melanoma); according to Taussig and Torrey, however, trauma is not always recorded preceding the onset of melanoma. A relatively rare localization is in the nail bed or nail fold (melanotic whitlow of Hutchinson). Pack and Adair (1939) found that 29 (6.1%) of 477 tumors occurred on the hand, and of these 34.5% were subungual in distribution. They list 13 conditions which must be differentiated from this lesion. Sometimes the lesions may arise on the conjunctiva and other ocular sites (reviewed by Reese, 1938 and 1943). Malignant melanoma may affect the nervous system. In their review of this subject Moersch, Love and Kernohan found 34 such cases (of which 19 were verified at autopsy) in 500 cases of melanoma observed at the Mayo Clinic from 1930–1939. In about one-quarter of the cases, the primary tumor was about the eye. In at least 347 cases of melanoma there was evidence of recurrence or metastasis at the time the patients were seen at the clinic. Most of them died, and in at least 34 of these 347 patients there was clinical evidence of central nervous system involvement. Netherton offers three possible explanations of the relation of the pigmentary changes in the meninges to the pigmentation on the skin: (1) melanoma of the meninges as a metastatic lesion coming either from the nevus or the eye, either being the usual location of primary malignant melanoma; (2) the lesions being of a different type, unrelated and only coincidentally associated; (3) the nevus and changes in the central nervous system being related in that they were congenital malformations resulting from widespread developmental disturbance in the ectoderm. He regards the third as the most plausible.

It is stated that about one-third to two-

thirds of the malignant melanomas arise from a pigmented nevus. This fact is substantiated by most authors (among them Montgomery;[193A] Butterworth and Klauder; Becker, Taussig and Torrey; Howes and Birnkrant and Traub;[305] Traub and Keil[306]). Those who claim they usually arise from normal skin may do so because of faulty observation on the part of the patient to notice a relatively insignificant spot or because the lesion may be occasioned by the presence of a congenital cell rest which remains quiescent until stimulated to active growth. On the other hand, there is disagreement as to the type of nevus which is the precursor of the malignant melanoma. Montgomery (1944) claims that contrary to what has been stated in the literature (Taussig and Torrey; Traub; Traub and Keil), they may arise from both the superficial flat or junction type of nevus and the ordinary hairy mole. We believe that if this latter phenomenon is possible, it must occur very rarely. Lentigo maligna, which is a deeply pigmented flat macule or slightly raised papule may remain as such or result in verruca senilis, senile keratosis or malignant melanoma. All types of transitions between various pigmented spots and nevi and malignant melanoma have been described.

The course of malignant melanoma is variable. It is well described by Butterworth and Klauder, and Montgomery.[193A] The first symptom of malignancy is a very rapid increase in size and the lesion may become verrucous, fungoid or ulcerative. Increase of pigment occurs at the same time or soon thereafter. Montgomery (1944) recognizes fine radiating lines of pigment extending up the lymphatics as indicative of extension. Bleeding also occurs early, but may not appear until some months after increase in size. Metastasis may occur early in the disease and may skip adjacent lymph nodes to show involvement of the internal organs. Multiple cutaneous metastases may be seen and, depending on the rapidity of growth, may be pigmented or not (amelanotic melanoma). Those from the eye are usually amelanotic. Eller and Schonberg[85] observed a patient with metastatic melanocarcinoma with apparent recovery. Histologically, this tumor is represented by the presence of malignant nevus cells. Biopsy may be necessary to rule out other blue black nodules which are not malignant melanoma.

Most authorities agree that electrocoagulation or cautery are dangerous and that radiation therapy is to be discouraged. Best results are obtained by radical excision, amputation if necessary, and dissection of lymph nodes, prophylactically (Peck and Adair; Howes and Birnkrant). There is much discussion and disagreement regarding the prophylactic removal of moles, but a safe guide would seem to us to be that since removal of all moles is impractical, those which are subject to repeated trauma, especially at sites of frequent occurrence of malignant melanoma (head and feet) should be removed by wide excision or through destruction as advised by Klauder.[142] Casual handling of this problem leads to what Tod has aptly termed the "tragedy of malignant melanoma."

An interesting note by Herbst[118] on "malignant melanoma of the choroid with extensive metastasis treated by removing secreting tissue of the testicles" was followed by a case of failure to cure melanoma by this means. A summary of the facts which link melanoma to the sex glands has been made by Howes.[127]

Connective Tissue Tumors. *Keloids.* These are benign, proliferative fibrous tissue overgrowths having their origin in the subpapillary plexus of the cutis and developing as a result of trauma. Keloids are fully discussed in the review of Garb and Stone.[95] Because they have distinctive characteristics, they occasion little difficulty in differential diagnosis from other benign growths. Histologic study is obligatory for final evaluation.

Histiocytoma Cutis. Fibrotic nodules of the skin have been studied recently by

numerous investigators: Sweitzer and Winer;[289c] Keil;[140] Urbach and Hill;[310] Michelson;[187] Traub and Monash;[307] Senear and Caro;[264] Stecker and Robinson;[273] Lewis and Sachs;[157] Bernstein;[31] Arnold and Tilden.[14] In their paper Sweitzer and Winer discussed the various types of fibrotic nodules which occur in the skin. They included nodules which appeared after trauma, and after certain general systemic diseases, subepidermal fibrosis and knuckle pads. We shall only discuss histiocytoma cutis (subepidermal fibrosis).

Histiocytoma cutis has been designated by a variety of names, including fibroma simplex, nodulus cutaneus, dermatofibroma lenticulare, dermatofibroma, nodular subepidermal fibrosis and by Urbach and Hill, imbibitio lipoidica collageni degenerati cutis. These tumors are of frequent occurrence; they may be single or multiple and are located mostly on the extremities but do not favor the region of joints. The sites of predilection are the extensor surfaces of the tibia and forearms, but any part of the body may be involved. They are small, superficial, hard, flat, asymptomatic lesions which range from about 0.5 to 3 cm. in diameter. Their color varies from red to dull brown, depending on their age. When removed, the lesions show no tendency to recur. Histologically Sweitzer and Winer "observed in all of them a circumscribed proliferation of the collagenous fibrils in the deep reticular cutis. The interfascicular spaces are compressed, obliterating the lymph spaces. Sebaceous glands are absent, and sweat glands below the involved area are atrophic or compressed. Histologically the lesion is stellate and contains few vessels in its substance. The periphery, although not encapsulated, stands sharply in contrast with the normal connective tissue which circumscribes it. At the junction of the normal and abnormal tissues the blood-vessels show marked sclerosis. The elastic tissue within the lesion is greatly diminished or entirely absent. One is impressed, except for the irregularity, by the similarity to a true scar." Michelson thought these lesions were a response of the connective tissue to a low grade excitant which does not bring about suppuration or liquefaction but results rather in scar formation similar to keloid. Sweitzer and Winer, by study of frozen sections using stains for fat and injecting saccharated iron (1%) into lesions, were unable to note any excessive presence of fat or iron granules in phagocytic cells, as mentioned by Senear and Caro. They agree with Stecker and Robinson that the histiocytes reported are probably wandering phagocytes and that the tumor itself is not a histiocytoma. Urbach and Hill likewise rejected the histiocytoma cutis concept for these lesions and thought their evidence favored the classification of these lesions in the category of a new local lipoid dermatosis "imbibitio lipoidica collageni degenerati cutis."

Arnold and Tilden studied 27 lesions and 23 patients. They concluded that histiocytoma cutis is a tumor resulting from sharply localized proliferation of cells which have the ability to, and usually the opportunity to, phagocytose lipids or other foreign material and are therefore of reticulo-endothelial system origin. Cells invade, damage and displace normal dermal collagen instead of producing new collagen. It is related to xanthoma group and not fibroma. Like xanthoma, it is probably related in some way to type of metabolic disturbance observed in diabetes mellitus. Histologic study is needed to differentiate from fibroma. They occur in women and men in a proportion of 5 to 1. Age and race are not important factors. About 50% of the cases had a close relative with diabetes. Of 22 cases, 15 gave a positive reaction for fat to the Sudan III stain. No typical foam cells were found except in 1 lesion. In 7 cases some cells resembled foam cells.

Oil Tumors. In 1920 Mook and Wander[202] described the occurrence of painful tender slowly-growing tumors in 6 patients who had been previously subjected to serious operations and had received

camphor in oil injections as a stimulant. Since then numerous studies of the tumor response to the injection of oils have appeared: Stokes;[278b] Burrows and Johnston;[43] Sutton;[284] Weidman and Jeffries;[326] Jorstad and Glenn;[138] Burrows and Jorstad;[44] Rosser and Wallace;[253] Conrad, Conrad, Jr., and Weiss.[60] These tumors induced by various oils (including liquid petrolatum, linseed oil, corn oil, sesame oil) are not in reality neoplasms, but represent foreign body reactions to the oil.

Hemangio-endothelioma. The designation hemangio-endothelioma (Mallory[176]) has been loosely applied to identify tumors showing similar clinical features but with variable microscopic findings. Sweitzer and Winer[289b] (1936), in their report of 6 cases and review of the literature, defined it as a tumor which may occur on almost any part of the body. Its size may vary from that of a pea to that of an orange. It is usually dark red and moderately soft and may or may not be surrounded by satellites. Some of their patients presented a large tumor. The neoplasm often ulcerates on trauma and bleeds profusely. It infiltrates and can attach itself to underlying tissue and bone or to the overlying skin. According to its site of development, it may at times form a pedunculated tumor. It is not tender and is not painful when manipulated.

Histologic structure: The tumor was considered in 3 related zones, each gradually fusing into the other without any definite line of demarcation. By this schematic method the explanation of the histologic picture is simplified. In the center of the mass are mature structures; progressing toward the periphery, the vessels gradually become more immature. Thus the central core consists of capillaries filled with blood. Surrounding this central core are solid cords or strands of cells which are in the process of forming lumens, while on the extreme outer border or periphery of the tumor are irregular masses of cells showing no features of differentiation. The individual cells are large and exhibit a clear cytoplasm and a nucleus that is small in comparison with the size of the cell. These cells are endothelial cells but cannot be recognized as such except when an embryologic capillary with a lumen is formed. Naturally, many cases vary in various ways from this description.

Stout[280e] required the presence of numerous atypical endothelial cells in excess of the number needed to line the vessels with a simple membrane and also the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose. Hemangio-endothelioma is to be differentiated from hemangioma, vascular sarcoma, granuloma pyogenicum tumors and Kaposi's disease.

Caro and Stubenrauch[50] in their careful report regard malignant vascular tumors as a rarity and think that the literature suggests that a large proportion of such malignant tumors belongs to the group of hemangio-endotheliomas. Diagnosis is not possible on clinical grounds alone, but depends on the demonstration of typical histologic changes (masses of atypical endothelial cells and vascular tubes, lined by several layers of endothelial cells and have a tendency for their tumors to anastomose). These authors produce a convincing summary of evidence indicating that trauma is an important factor in the production of these lesions.

Von Recklinghausen's Disease (*Neurofibromatosis*). Von Recklinghausen's disease is a process of varied clinical character. Its most frequent and almost constant feature is the presence of multiple cutaneous tumors (molluscum fibrosum), which vary within wide ranges in extent and size. These lesions do not show evidence of localization corresponding to that of the peripheral nerves. In addition, pigmentary disturbances of the skin are numerous and frequently precede the appearance of the tumors. These appear as various sized macules and plaques. There may be tumors of the central and peripheral nervous systems

and of the viscera, associated anomalies of bones and possibly endocrine disturbances. Low standards of physical and mental standards have been reported by various writers (Charpentier;[53] Ormsby and Montgomery;[216] Levin and Behrman).[154] Based on histologic evidence, many authors (summarized by McNairy and Montgomery)[183] have described the presence of nerve fibers in lesions of the peripheral nerves. The histologic picture of cutaneous tumors is less definite. They are sharply circumscribed and have a structure distinct from that of the adjacent cutis. They are described as being composed of peculiar nucleated bands of pale, fine, spindle shaped fibrillæ resembling those seen in nerve tissue. The absence of elastic tissue has been observed. The presence of nerve fibers has been reported by some authors and denied by others. McNairy and Montgomery have collected the literature on this point. Because of the uncertainties regarding the presence of nerves in these cutaneous tumors, McNairy and Montgomery reported on a histologic study of the problem based on 15 cases and on a search for nerve fibers by Bodian's method of staining.[183] In 12 cases, non-medullated nerve fibers were clearly demonstrated. This supports the thesis that these lesions are true neurofibromata which arise from the peripheral nerves and their supporting structures and that these nerve fibers are peripheral extensions of the nerve bundles which have been included in the expanding nerve sheath tumors. The cutaneous tumors of von Recklinghausen's disease thus may be said to have a specific histologic architecture and are thus readily distinguished from other cutaneous tumors or from the tumor-like macular atrophy of Schweninger and Buzzi. Pigmented macular lesions (2 studied) showed no histologic evidence of an underlying neurofibromatous structure or of an increase in nerve fibers.

Thannhauser[296] recently presented an exhaustive study and revaluation of the apparent relations of neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica. On the basis of reports of simultaneous occurrence of nodular cutaneous neurofibroma, pigmented areas of the skin and osteitis fibrosa cystica in a single patient, a relationship between neurofibromatosis and osteitis fibrosa cystica is suggested, since the occurrence of these symptoms of 2 rare diseases in 1 person cannot be mere coincidence, according to Thannhauser. Fibrocystic involvement of localized areas of the skeleton, especially the long bones, occurs in neurofibromatosis together with *cafe au lait* spots and cutaneous neurofibromas. Although microscopic examination of the osseous fibroma does not reveal nerve structures within the fibroma, whorls of spindle cells are occasionally found and may be thought to reflect its neurofibromatous origin. Thannhauser believes that hyperpigmented areas are the expression of underlying neurofibromatosis even without the appearance of neurofibromatous nodules. The presence of similar endocrine symptoms, especially the concurrence of precocious puberty and pigmented blotches of the skin in neurofibromatosis and also in osteitis fibrosa cystica disseminata offers additional corroboration of the belief that the 2 disturbances are related. This suggests that the anatomic structures which underlie the endocrine symptoms in cases of simple neurofibromatosis are the same as those of osteitis fibrosa cystica disseminata (von Recklinghausen).

Cutaneous Neuroma. This exceedingly rare lesion has been the subject of study by Ludy[169] and by Montgomery and O'Leary.[200] This type of tumor is a lesion which contains abnormal growth nerve elements and has its location and development in the true skin. They are distinct from the nevi containing lesions of von Recklinghausen's disease. The nodules are painful and may be incorrectly diagnosed as some granuloma such as tuberculosis clinically. Montgomery and O'Leary carefully reviewed the literature on this subject and described a heretofore unrecognized process which they called

multiple ganglioneuroma of the skin. The disease consisted of discrete, firm, yellowish papules or nodules of from 1 mm. to 1 cm. in diameter. During their development the reddish brown color of the lesions suggested sarcoid or tuberculid. The lesions first appeared on the buttocks, later spread to the trunk and extremities. The healing of lesions was followed by the development of new lesions. The entire disease had left the patient without a trace within 3 years. Histologically the condition was characterized by the presence of numerous large pale staining ganglion cells.

Kaposi's Disease (*Multiple Idiopathic Hemorrhagic Sarcoma*). In 1872 Kaposi described the process now generally called Kaposi's sarcoma which he called multiple idiopathic pigmented sarcoma at first, and later multiple idiopathic hemorrhagic sarcoma. Excellent recent publications dealing with this subject are those of Dörffel;[76] MacKee and Cipollaro;[172a] Becker and Thatcher;[24] Symmers;[290] Aegerter and Peale;[6] Nesbitt, Mark and Zimmerman;[205] Sachs and Gray.[256]

A concise description of the lesions of this disease is given by Aegerter and Peale[6] as follows:

"The disease is most commonly primary in the skin, though the primary process has been reported in almost all parts of the body. It was the cutaneous type which Kaposi described. The lesion usually begins as a reddened macular area on an extremity, most commonly a lower extremity. The edges are usually definite but there is no characteristic shape. The macule varies greatly in size, depending on how long it has been present. As the lesion progresses, the color of the involved area darkens, becoming first dusky red, then bluish and finally brown or black. This change of color is understandable after microscopic study of the lesion. At first there is an increase in the supply of blood to the part through the cavernous vessels. At this time the area is livid. But as the cellular elements of the tumor increase, there is stagnation of the blood, and finally hemorrhage with rather remarkable pigmentation, which probably results from the disintegration of the blood. The involved area soon becomes elevated and in the early stages resembles a varicosity. As the tumor ages, becoming more cellular and less vascular, it becomes firm, and its appearance is that of a true neoplasm. The lesion rarely regresses spontaneously, although it may remain stationary for months. Healthy areas of skin proximal to the lesion may soon become involved. The older lesion may fade out, become keratinized and present a scaly surface. The subcutaneous tissues become infiltrated, and the lymphatics are frequently blocked, causing an immense edema, even elephantiasis, of an extremity. Sometimes the lesions are pruritic, and trauma may cause them to bleed freely. Sooner or later, lesions usually appear in the viscera. Some writers believe these to be spontaneous multiple primary growths because they are able to find all the stages of development in these lesions. If we accept the opinion that this disease is cancer from the outset, and such is our premise, we may regard these secondary lesions as metastases, following the usual course of cancer. Death may occur from infiltration of the lungs, the liver or the spleen but by far the most common sequence is metastasis to the intestinal mucosa with ulceration causing hemorrhage and exsanguination. When the tumor is primary in the viscera, it is usually not found in the skin. . . . Metastasis to lymph nodes is not general, but it occurs, and the metastatic lesions reproduce the primary cellular picture.

"If sections are made of the very early lesions in the skin, the microscopic picture is that of cavernous hemangioma. The sinuses vary in size and shape, they contain blood and they are lined by normal appearing endothelial cells. No perithelial cells could be distinguished in any of our slides. As a lesion progresses, it is seen to penetrate into the surrounding normal tissues, splitting muscle bundles and infiltrating the fat. This is seen in the very early lesions. The sinuses are less perfectly formed at this stage, and they are surrounded by masses of fusiform cells without pattern, the nuclei of which are indistinguishable from those of the endothelial lining cells. A little later the sinuses become indistinct and are represented by spaces which are filled with blood.

There are hemorrhage and considerable red cell degeneration, as shown by the quantities of pigment which take the iron stain. The endothelial lining is now almost indistinguishable, and there is an apparent transition of the endothelial into the fusiform cells. The latter cells proliferate to form masses, some of which are quite avascular. Sections through these areas are easily confused with fibrosarcoma or even neurogenic sarcoma. These solid masses occupy the corium, pushing upward to flatten the papillæ, causing thinning of the epidermis. It is these masses that give rise to the nodular gross appearance. By this time there is usually an inflammatory reaction, as shown by an infiltration of lymphocytes, plasma cells and a few macrophages. This may be accounted for by the hemorrhages. Differential stains give the staining reaction of young fibrous tissues. In some tumors these cells show definite malignant characteristics. In some instances the solid cell masses have the appearance of endothelioma. The cells are polyhedral and arranged in sheets about irregular sinuses, some of which contain erythrocytes.

"The duration of the disease varies from 8 months to 25 years although in the majority of instances the process terminates after 5 to 10 years. In a few cases it has been reported to have regressed, with the patient remaining free of symptoms for a number of years. We are tempted to question the diagnosis in these cases since by far in the majority of over 600 reported cases the disease was progressive, though sometimes remittent in character."

The nature of this disease has been considered to be sarcoma, granuloma of nerve tissue or a blood-vessel and lymph vessel disorder of the nature of angioma, hamartoma, connective tissue proliferation with vascular dilatation, proliferation of sympathetic perivascular nerve fibers, or reticulo-endothelial system disease with a disturbance in its monocytogenic function. Becker thought that the most logical explanation of Kaposi's sarcoma was that it is a multicentric benign neoplasm originating in the perithelial tissue from embryonic mesenchymal cells (lymphocytoid cells of Marchand), which results in a type of cell growth unique for the disease. Aegerter and Peale thought it was a vascular cancer. Symmers thought that the unit of growth in the cutaneous nodules of Kaposi's disease is the fibroblast.

Becker lists 36 synonyms for the disease. The cause of the process is unknown. It is presumed to be a toxic or infectious substance which acts on the vascular system with resultant inflammatory reaction, vascular dilatation and subsequent proliferation of the vascular wall elements. Dillard and Weidman[73] found fungi resembling *Achorion schoenleinii* in the lesion, but did not believe them to be pathogenic. Greco[108] found an organism of the cryptococcus type. The relationship of this to the origin of the disease is unproven. The disease occurs chiefly in Italians and Hebrews. Ellis[86] reported a case in an American Negro. It occurs chiefly in persons between 50 and 70 years of age. Men are the chief sufferers. In addition to the cutaneous lesions there may be lesions in the gastro-intestinal tract, liver, lungs, abdominal lymph nodes, spleen, pancreas, kidneys, suprarenals, testes, epididymis, trachea, thyroid, bronchi, pleura and heart muscle. The nervous system is rarely affected but Nesbitt and his coworkers reported lesions in the brain.

Nevi. Nevi are, in the broad sense, any congenital circumscribed new growth, but the term is commonly used as synonymous for ordinary cellular nevus (mole). In a learned paper Meirowsky[184] discusses the inheritance of nevi and other malformations of the skin; he concludes that man has become prone to nevi and malformations of the skin by the factors both of domestication and phylogenesis. A convenient classification of the various types of nevi is that of Traub:[305]

I. Vascular Nevi.
- A. *Nevus vasculosus* (hyperplasia of blood-vessels).
  1. Flat (capillary). Example: nevus araneus of nevus flammeus.
  2. Raised (capillary). Example: angioma.

I. Vascular Nevi.—(*Continued*).
   3. Deep (capillary). Example: cavernous angioma.
   B. *Nevus lymphangiectodes.*
   C. *Nevus vasculosus et lymphangiectodes.*
   D. *Heterogeneous vascular nevus.* Example: combination of the above types in the same mark.

II. Pigmented, Hairy and/or Warty Nevi.
   A. *Intra-epidermal nevus* (no nevus cells). May terminate in basal cell or squamous cell epithelioma. Possible examples:
      1. Nevus verrucosus (hard). May also present some hairs or pigmentation, and frequently has a linear configuration.
      2. Verruca senilis or keratoma senile. Generally becomes basal cell epithelioma if a change takes place at all.
      3. Dermatosis papulosa nigra.
   B. *Epidermo-dermal nevus* (junction type nevus). Nevus cells present. May terminate in melanoma (nevocarcinoma). Example: Nevus pigmentosus. May rarely also present a few fine, or *sparse* coarse hairs or have a *soft* warty surface.
   C. *Intradermal nevus* (nevus cells present). Benign always, if pure type. Example: Nevus pigmentosus et verrucosus et pilosus. Always soft and warty in character—not hard.
   D. *Blue nevus* (cells of different shape than in preceding types). May rarely terminate as melanosarcoma.
   E. *Heterogeneous pigmented nevus* or combination or mixture of two or more of the above types (nevus cells present). May terminate as basal cell or squamous cell epithelioma, as melanoma or melanosarcoma.

III. *Nevi of Special Tissue.*
   A. *Glandular* (sudoriparous gland nevus, sebaceous nevus).
   B. *Connective tissue.*
   C. *Fat tissue*—nevus lipomatodes.
   D. *Nerve nevus.*
   E. *Heterogeneous type.*

Vascular Nevi. Vascular nevi have been discussed in a number of papers (Lister;[161] Vohwinkel;[314] Touraine and Bupperat;[303] Oughterson and Tennant.[220] The reader is referred for a complete discussion of the question of spider angioma (*Nævus araneus*) to the excellent monograph by Bean.[22]

Pigmented Hairy and/or Warty Nevi. Traub in 1941 described in some detail the clinical features of the nevi mentioned in his classification. The intra-epidermal nevus consists of lesions that lie entirely within the epidermis and are formed by proliferation of a mixture of normal prickle and basal cell type epithelial cells. There are no nevus cells. Clinically the lesions appear to be superficial, contain a variable amount of pigment, and may assume a linear configuration. They rarely terminate in cancer. Evidently Traub is using this term for what we commonly speak of as seborrheic verruca or senile keratosis. Waisman and Montgomery,[329] in their discussion of verruca plana and epithelial nevus, used the latter term for verrucous and papillomatous nevi which were first systematically classified by Unna, under the designation "hard nevi," in which group he included circumscribed warty protuberances with the microscopic appearance of purely epithelial thickening. Unna described the lesions as being clinically hard, flat, pink to gray or dark brown and of variable size, from that of a lentil to that of a pea, the surface being rough or finely granular. Histologically, he distinguished 3 types, determined by the site of epithelial proliferation, as the keratoid, the acanthoid and the mixed or combination form. Of Unna's 3 types, 1 or possibly 2 were verruca senilis, a lesion which may be a delayed epithelial nevus with distinctive histologic picture. Examination of certain epithelial nevi, of both the circumscribed and the linear form, indicates that pathologic changes may be present which are practically identical with those present in epidermodysplasia verruciformis. The vacuolar protoplas-

mic abnormality which each form manifests indicates the essential nevoid structure common to them. Under the designation "mole," Traub regards a cellular nevus characterized histologically by the intracutaneous arrangement of nevus cells in special configurations (nests, bands and strands). Nearly all such lesions show the presence of a variable amount of melanin pigment both clinically and histologically, but this item is not obligatory. These growths may be present at birth or appear shortly after birth or later in life. From a clinical standpoint there are all sorts of transitions between various types of nevi. This complicates the problem because it brings up the question of possible transitions in type between the epidermodermal and intradermal nevi. The junction type clinically (Traub) "is the relatively flat or slightly raised smooth pigmented mark that is devoid of coarse hairs. Hairs are usually entirely absent, but fine (lanugo) hairs or occasional coarse sparse hairs may be observed both clinically and histologically. As a rule, the hairs are never a striking feature, as most of these marks are described as devoid of hairs. The surface is usually smooth, but as the lesions get older or take on added growth, they may develop an irregular or even soft verrucous or fungating surface. The size may vary from a tiny mark no larger than a pinhead to one of considerable dimension, but the largest marks that I have so far encountered have not been over 3 to 4 cm. in diameter and the majority do not exceed 1 to 3 cm. in diameter. They are found most commonly on the extremities and the face—less frequently on the trunk—but they may occur anywhere. On the trunk the most frequent location seems to be the upper back (shoulders) and the next the abdomen."

Traub and Keil[306] define the histologic features of the "common mole" as:

"1. Intra-epidermal nevi lie entirely within the epidermis and present a proliferation of normal epithelial cells, a mixture of prickle and basal cell type, not referred to as nevus cells. They may or may not be pigmented. They rarely terminate in cancer.

"2. Intradermal nevi are probably the most frequently encountered lesions and are characterized by the occurrence of nevus cells arranged intracutaneously in nests and strands. The cells are of the mature type, and to become malignant they revert to the embryonic type. Pigment is generally present in varying amounts. Cancer of malignant melanoma rarely, if ever, occurs.

"3. In junction type nevus (Satenstein) or borderline melanoma Becker stated: 'The process may be interpreted as hyperpigmentary due to an increased number of melanoblasts at the epidermo-dermal junction.' The cells are not separated from the epidermis, as in the intradermal nevi, in which the nevus cells are seen in nests or strands usually detached from the epidermis. The cells in this type are of the embryonic (anaplastic) type, and the lesion constitutes the forerunner of the malignant melanoma. The criteria necessary to decide whether a junction nevus has definitely become a malignant melanoma require careful consideration of both the clinical picture and the course of the lesion, as well as a minute study of the histologic changes. Lesions are encountered which clinically seem innocent and which apparently pursued a benign course as long as we have been able to keep the patient under observation. But the reports on slides studied in these cases by various pathologists show great differences of opinion. If a report of malignant melanoma had been accepted in such cases without due consideration of the innocent clinical course, great harm might have been done. We believe that the clinical criteria for malignant melanoma have been sufficiently stressed so that it would be superfluous for us to restate them, but the histologic grounds or basis for such a diagnosis certainly seem less clearcut.

"It appears logical that the following points are necessary for the diagnosis of malignant melanoma: (1) 'trickling off' and segregation (development of théques) (one of the principal changes and found without difficulty), (2) the presence of clear cells, which may resemble the Paget cells, (3) mitotic figures (generally readily found), (4) chronic inflammation. The more evident each of these changes appears in the

section, the more certain one may be of the malignant nature of the growth.

"4. The combination type nevus represents a combination of Types 1, 2 and 3.

"5. The blue nevi (slate blue or grayish blue), which are chiefly found as isolated lesions on the face and dorsum of the hands, have no relation to melanoma. The color is apparently determined by the number and depth of the melanoblasts. It must be emphasized that the name blue nevus should be restricted to pigmented growths composed of a peculiar type of connective tissue cells apparently capable of forming melanin; that so far as the literature and our limited observations are concerned these spots are benign in their course, that that diagnosis on the basis of color alone is unreliable, as other lesions, such as the melanoma and the 'common mole,' may reveal similar shades of blue. In rare instances an ordinary intradermal mole may show clinical features apparently indistinguishable from those of the blue nevus; this phenomenon is apt to occur when the nests of nevus cells and their accompanying pigment are separated from the epidermis by a wide stretch of intervening connective tissue. It is interesting that a number of cases have been recorded in which the characteristics of an ordinary mole were associated more or less intimately with those of the blue nevus of Tieche. This represents another example of a combination of nevi. It has been claimed that blue nevi may terminate in sarcoma, but such a change must be rare indeed, for Satenstein, Becker, Peck, Ewing, Wood and Fraser have not seen examples of it." (Blue nevus will be discussed below.)

Montgomery and Kernohan[198] made an intensive study of pigmented nevi. The nevus cell of the common ordinary pigmented nevus has been maintained by various authors to originate from single and from multiple sources. Origin from basal or dendritic melanoblastic cells in the epidermis (Kissmeyer; Miescher; Perin), mesodermal origin from connective tissue cells of various types, including also origin from the adventitia of the blood-vessels (Stoeckenius), origin from the lymphatic endothelium, multiple neuro-epithelial points or origin from "celules claires" in the epidermis, cells of Schwann sheaths, neuroid tubes and true nerves in the deeper part of the cutis (Foot; Masson; as well as from peri-endoneural endothelium of the skin (Feyrter) have been included. Close relationship, if not even origin, of nevus cells from the walls of hair follicles, from sebaceous glands and even from the endothelial cells of the intima of the blood-vessels have all been described (Ebert; Gans; John; McCarthy). Since Masson's articles an increasing number of pathologists have tended to accept multiple neuro-epithelial points of origin for the nevus cell (Becker; Ewing; Foot).

Recently John described a "drop" cell in the middle layers of the epidermis which he called a stalagmocyte. He distinguished this from the Langerhans cell and the dendritic cell and assumed that stalagmocytes play an important rôle in the formation of nevi. Multiple and varied clinical and histologic classifications of different types of true nevi are given in recent articles in the literature, most of which also include extensive reviews of Masson's theory and other theories regarding the origin of nevi (Becker; Broders; Ebert; Foot; Laidlaw; Traub; Zeisler).

Montgomery and Kernohan studied a group of 460 nevi in which ordinary nevus cells (histologically) with special reference to the neuro-epithelial origin of the nevus cell as advocated by Masson and also in regard to diagnosis, prognosis and treatment. Various special nerve and trichrome stains and also stains for pigment reticulum fibers, etc., were employed for many of the nevi. In only 11% was there evidence of *lames foliacées*. Origin of nevus cells from the epidermis was demonstrated in a majority of cases. In many instances the nevi apparently arose from cellules claires, but in others from basal or dendritic cells. The question is raised as to whether cellules claires may not represent altered forms of basal or dendritic cells. The histologic evidence would support Unna's older conception of epidermal origin against Masson's con-

ception of neuro-epithelial origin of the nevus cell. Cellules claires can be identified readily in formalin-fixed sections even with hematoxylin and eosin stain but better with Masson trichrome stain. Distinction between fine strands of melanin pigment in dendritic processes of melanoblastic cells and true nerve fibers in the epidermis may be exceedingly difficult as silver stains all stain melanin pigment.

The many cases of superficial flat nevi and lentigines in which histologically nevus cells are present and in which there is no increase in cutaneous nerves or nevus cells deeper in the cutis, would tend to refute a neuro-epithelial origin for the nevi. This is especially true if the cellules claires are regarded as melanoblastic cells rather than modified tactile cells of Merkel-Ranvier. On the basis of our studies we are strongly inclined to support Unna's old concept of an epidermal origin for the majority of the nevi, admitting a nerve origin for about 15% of the cases in which *lames foliacées* are present. Just as we see multiple types of nevi in the same individual, so multiple points of origin for the nevus cell might be expected, inasmuch as we are dealing essentially with a malformation. In our series of 460 nevi, 1 instance of apparent origin of nevus cell from sebaceous cell was seen and in several instances, nevus cells apparently were intimately connected with, if they did not arise from, the endothelium of the capillaries of a hemangioma.

The question of malignant change in pigmented nevi merits discussion. Superficial nevi (so-called junction nevi) in which collections of malignant-looking nevus cells are limited to the upper portions of the cutis or occur as intra-epidermal nests (*théques*) and in which the condition is suspected histologically of being early melano-epithelioma usually offer a good prognosis. These nevi should be distinguished from cases of frank melano-epithelioma in which the prognosis is almost invariably serious, at least almost invariably so when there is histologic evidence of invasion of the lymphatics by the tumor cells.

Pigmented nevi should not be confused with blue nevus or with verruca senilis. Pigmented nevi, whether superficial or deep, papillomatous or verrucous, or slightly to deeply pigmented, need not be removed except for cosmetic purposes unless they are subject to repeated trauma and irritation. Surgical excision is the method of choice. Partial removal of superficial fulguration, electrolysis, the use of solid carbon dioxide or caustics, although apparently satisfactory in the hands of many dermatologists, in our experience have the potential danger of subsequent development of malignant epithelioma in a small percentage of the cases. Radium and Roentgen therapy in any form is to be condemned vigorously.

Finally, as to nevi, Montgomery and Kernohan have stated that the nevus cell probably has multiple points of origin but that origin from the epidermis, as Unna originally emphasized, predominates. Evidence of a neuro-epithelial origin with the presence of *lames foliacées* occurs in 10 to 15 or possibly as high as 20% of the nevi. Origin from the outer walls of hair follicles may be anticipated in view of the predominant epidermal origin. The rare instance of origin of nevus cells from sebaceous glands and an occasional intimate relationship of nevus cells to the endothelial cells of the capillaries are illustrated in this article.

Ebert[78] suggested that the cellular type of nevus is formed from many elements, blood-vessels, histiocytes, connective tissue cells, nerve fibers and various other cells. The nevus cell is the unique element, and a study of its origin has been the primary object of Ebert's study. It is the parent cell of the malignant melanoma. Greenblatt, Pund and Bernard[110] present a schematic outline of the histologic findings in the gradual transition of the benign nevus to the malignant melanoma. Arnold[13a] reported a case of multi-

ple tardive pigmented nevi, unusual clinically in that the apparently mature lesions showed a tendency to central papule formation, and histologically in that these same seemingly mature lesions showed only beginning extension of nests of nevus cells in the corium.

The Blue Nevus. The blue nevus was first identified by Tiéche[298] in 1906. This is a fairly frequently seen lesion in spite of the relative inattention which has been accorded it. For example, Becker[23a] does not mention it in his valuable paper on melanotic neoplasms of the skin. Undoubtedly it has been mistaken for early malignant melanoma because of the slate black color. It remained for Montgomery and Kahler[197] to describe completely the process for the American literature and for Traub[305] to further indicate the relative position of this benign growth among the various types of pigmented and hairy nevi. For details and for a summary of the literature the reader is referred to these papers; but the essential facts regarding it have been summarized by Montgomery[193a] as follows (see also above):

"Blue Nevus. I believe blue nevus to be a relatively common disease as I have encountered more than 100 typical cases. I believe that in the past it has been confused with melano-epithelioma and nevus pigmentosus. Blue nevus is a sharply circumscribed, smooth, round or oval, indurated papule or nodule usually varying from 2 to 15 mm. diameter, occurring most frequently on the face and hands but to be found anywhere on the body. The color varies from dark or mottled blue to blue black, blue gray or even steel blue. There usually is a history of a solitary lesion which either has been present since birth or developed in infancy or early childhood and which has remained as such without increase of size. Such a history is diagnostic. Two or more lesions sometimes occur in the same case. Occasionally, blue nevi develop later in life, and, when they are steel blue and have increased in size, they may be indistinguishable clinically from a melano-epithelioma. Wide excision and histopathologic examination then are indicated.

"Blue nevus is characterized histopathologically by well-formed, mature, dermal, dopa positive melanoblasts having long bipolar dendritic processes laden with melanin pigment. Such melanoblasts are found in smaller numbers in so-called Mongolian spot. Mongolian spot is much larger than blue nevus and occurs as an ill-defined, bluish to mulberry colored or blackish plaque, usually in the vicinity of the sacrum. It is present at birth but usually disappears in the third or fourth year of life. Blue nevus is a benign lesion and only exceptionally, following repeated trauma and inflammation, does it undergo malignant change. In such cases it forms a true melanosarcoma rather than a melano-epithelioma."

Connective Tissue Nevus. Steiner[274] in a scholarly article reviews the knowledge of this rare nevus. It is a lesion consisting of papules or lichenoid nodules varying in size from a pinhead to that of a millet seed, and in color from snow white to brownish. The nevi are usually single. They are usually located on the chest, usually the upper third. In almost all cases, the nevi attracted attention because of their systemization, usually in bands, sometimes in zosteriform arrangement. They are usually asymptomatic. Histologically there are epithelial changes in some of the cases; but the characteristic, and usually the only, changes are in the cutis. All authors agree on the fact that there are changes, but there is disagreement as to the degree of involvement of the collagen or the elastic tissue. Steiner states that the changes are usually homogenization and hypertrophy and sometimes apparently an altered arrangement of the collagenous tissue. There is elastorrhexis, elastoclasis and atrophy of the elastica. Rarely there are atrophic changes of the collagen fibers. Collagenous and elastic tissue alterations can be observed in the same case or independently of one another. The changes are mostly in the upper cutis. These cases must be differentiated, especially from lichen albus, scleroderma in bands, white spot disease and post-zosteriform scars. Pseudoxanthoma elasti-

cum may be difficult to differentiate from fibrous nevus.

Nevus Unius Lateris. Linear nevus, an interesting type of nevus known by a variety of names, has been the subject of numerous investigations. Pack and Sunderland[222] who have collated the important literature on the subject describe it as "a papillary or verrucous congenital tumor having a unilateral or nearly unilateral distribution in linear streaks or bands following the long axis of the limbs or extending transversely around the trunk. This unique disease is so striking that it is readily recognized as a distinct clinicopathologic entity." It is rare, these authors having found 4 cases among 20,000 patients with tumors studied at the New York Memorial Hospital for Cancer and Allied Diseases (0.01%).

The cause and pathogenesis of nevus unius lateris are still unsatisfactorily explained. The relationship of this process to the nervous system is still an unsettled question. It is probable from Pack and Sunderland's work that the primary involvement is in the epidermis rather than the dermis. The matter of malignant degeneration of nevus unius lateris needs further study.

A variety of unilateral nevus especially interesting to dermatologists is nevus unilateratis comedonicus (nevus follicularis keratosus of White), which Sweitzer and Winer studied.[289a] It is characterized by comedones unassociated with acne vulgaris, occurring in bands or groups. They are unilateral and in some cases accompanied by suppuration and scarring. Sweitzer and Winer did not feel that this was a variety of sebaceous gland nevus. Histologically, this dermatosis shows markedly dilated follicles filled with a keratinized material with many cysts having their origin in the follicular wall. We have just encountered an exquisite example of this rare type of nevus, in a Negress, extending in the midline from the umbilicus to the pubis.

Nevo-xantho-endothelioma. This lesion has been ably discussed in a well-documented paper by Lamb and Lain.[149] Adamson[5] in 1905 reported a case before the Dermatological Society of London which was classified as "congenital xanthoma multiplex" in a child of 2½ years. The lesions were for the most part yellow in color, although some had a decided reddish tinge. One on the neck had the appearance of vascular nevus, but on pressure showed a yellow base. Adamson also referred to a case of xanthoma multiplex developing from vascular pigmented nevi reported in 1888 by Kabner.

McDonaugh in 1909 and 1912 described multiple growths of the skin seen at birth or in early childhood which are characterized by their red angiomatous appearance at first, later developing a distinct yellow color and which tend toward a spontaneous involution. They are nevi. Since primary tumor cell in histological studies is related to those cells which form the capillaries and because of the finding of the peculiar endothelial giant cells, he suggests that the tumor be called an endothelioma, though it is not a true endothelioma.

Cases were reported by: Wise; Jacobi and Grand; Goldsmith; Dowling; McGraw; Senear and Caro; Montgomery. Lamb and Lain report a case and conclude that nevo-xantho-endothelioma, while not an accurate term, is fairly descriptive of a congenital malformation in which one encounters peculiar endothelial giant cells, as well as xanthoma cells, histiocytes and fibroblasts, with clinical spontaneous involution of the lesions in later childhood. Lamb and Lain's case is peculiar because of apparent systemic involvement without exophthalmus, diabetes insipidus or membranous bone manifestations. There is a link between cutaneous xanthoma and Hand-Schüller-Christian's disease. The embryonal cell rest theory for formation of this type of xanthomata is stressed by Lamb and Lain.

Osteoma Cutis. Variously known as osteoma cutis, osteosis cutis, osteomatosis cutis, chondro-osteoma, miliary osteoma and various other designations, this tumor

is regarded by Vero, Machacek and Bartlett[313] in their scholarly paper as one of the rare developmental abnormalities of the skin: Osteomas are benign new growths composed of bone and osseous tissue; they occur in most organs, including the skin. Secondary osseous changes may occur in certain cases of syphilis, in nevus, in response to trauma, in scleroderma, in acne vulgaris[124] and in multiple sebaceous cysts;[252c] but the spontaneous (primary) variety is rare. Clinical diagnosis is rarely made without biopsy, but Vero and his co-workers suggest that roentgenograms may be of aid in the diagnosis, as they may detect lesions which might otherwise escape inspection and palpation. These lesions appear in both sexes, especially on the scalp, forehead, cheeks and chin. They may be solitary or multiple. The color, size and shape give no real clue to the nature of these lesions. It is only when bone particles spontaneously extrude or histologic or Roentgen ray study is made that this true nature can be identified.

Mesenchymoma. Tauber, Goldman and Barrett[294] described a case of a new type of primary tumor of the scalp. It was highly invasive locally and gave rise to metastasis in the ribs and kidneys. It was not an ordinary tumor, and, because the tumor cells were so young and so undifferentiated, the term "mesenchymoma" was applied.

Leiomyoma. These tumors have occasioned much interest in the past. For example, Stokes[278c] in 1923 described a case of nevoid hyperplasia of non-striated muscle of arrectores pilorum associated with nevus pilaris. Stout[280b] reported 15 cases (7 in males) of solitary cutaneous and subcutaneous leiomyoma; none were diagnosed prior to biopsy. The origin of the smooth muscle in these tumors is the arrectores pilorum, the muscular apparatus in the depths of the skin or the muscles of the blood-vessel walls. They are of small size and grow slowly. Unlike the multiple form (mostly in males) the solitary form occurs equally in both sexes. More than half originate in middle or late life. The extensor surfaces of the extremities, the scrotum, labia, nipples or cheeks are the commonest sites. They are painless at first, but as they grow they become painful and tender. The pain is spontaneous or may be favored by fatigue, exposure or trauma. Contractions of smooth muscle in the tumor may result in pain. Nerve fibers have been demonstrated by Cajal's method. Most of the tumors are vascular or angiomatous, although the vessel network is never rich. Only 5 of 70 reported cases showed malignant tendencies. The tumor is elevated, never pedunculated and does not discolor the skin. Diagnosis depends on histologic study. Surgical excision is the treatment of choice, but Roentgen ray, electrocoagulation or cautery have been successful.

Myoblastoma (*Granular Cell Myoblastoma*). While not generally considered among cutaneous tumors, myoblastoma—a tumor composed of immature skeletal muscle elements—has some interest to the dermatologist because of its resemblance to xanthoma clinically and to carcinoma of the tongue histologically. The first report of such tumors was that of Abrikossoff[2] in 1926. Since then a number of reports have appeared and the more recent of Klemperer,[143] of Horn and Stout,[126] and of Crane and Tremblay[66] are worthy of study.

Clinically these tumors are small (1 to 2 cm. average), sharply circumscribed or encapsulated. They are benign but some may be poorly demarcated and irregularly penetrate the underlying tissues. Some of the lesions may present ulceration, some hyperkeratosis and others malignant epidermal proliferation. The lesions are usually solitary. Microscopically, the tumors are characterized by large polyhedral cells, the majority being irregularly rounded, but transitional forms having a tear-drop or spindle shape may also be present. The most characteristic feature of the cells is the cytoplasm which is abundant, acidophilic and granu-

lar, not vacuolated. Lipoid stains give negative reactions. Longitudinal and cross-striations have been demonstrated in some cases. The nuclei are small and vesicular, centrally placed, round or oval and associated with numerous pyknotic forms. An interesting feature is the hypertrophy of the overlying epidermis noted originally by Keynes (*Brit. J. Surg.*, 13, 570, 1926) and emphasized among others by Klemperer. They occur at all ages and with equal frequency among males and females. About half the cases occur in persons less than 50 years of age. They are widely distributed over the body but especially in the tongue and mouth. They may occur at sites containing skeletal muscle as well as those free from this tissue. Excision usually effects cure. The nature of the tumor is unknown but they are probably myoblastic or degenerative.

Glomus Tumor. The first case of this interesting lesion was described in 1878 by Kolaczek,[146] who called it angiosarcoma. Masson's original description of the glomus tumor in 1924[179] and Popoff's[235] subsequent careful studies on the distribution and alteration of the normal cutaneous glomus in peripheral vascular bed lesions stimulated interest in this subject. The first cases were reported in the American literature in 1934 by Mason and Weil,[178] and by Adair,[3] and by a Japanese in 1934 (Aisu[7]). This tumor has been variously called: angioneuroma, angiosarcoma, glomus tumoralis subungualis, Popoff tumors, tumors glomique, tumeur du glomus, neuromyo-artériel, subcutaneous painful tubercle, angiomyoneurome, angiomyo-neuroma of Masson, subcutaneous glomal tumor, angioma perithelioma, false neuroma, glomangiomas, and neuromyo-arterial glomus. Good reviews of this subject which have recently appeared are those of Raisman and Mayer;[245] Stout;[280a] Burman and Gold;[42] Bailey;[17] Lewis and Geschickter;[156] Cole and Sroub;[57] Jirka and Scuderi;[135] Hval and Nelson;[131] Theis;[297] Weidman and Wise;[327] Bergstrand;[29] Freudenthal, Anderson and Weber;[93] Slepyan;[269a] Radasch;[244] Grauer and Burt;[106] Davies, Hellier and Klaber;[70] Ostrowski;[219] Slepyan;[269b] and Love.[166]

Glomus tumor is not common. Streitmann[281] was able to collect (1933) only 21 cases which could be identified with this lesion definitely. Lewis and Geschickter report dealt with 17 cases from Johns Hopkins Hospital since 1924. Mason and Weil collected 34 cases; Adair, 10 cases; Stout, 11 cases; Bailey, 7 cases; Jirka and Scuderi, 70 cases, from the literature including their case (1 case in 7000 surgical specimens at Cook County Hospital); and various authors, 1 or 2 cases. We have encountered 5 cases among 2500 biopsy specimens from cutaneous lesions studied in the Hospital of the University of Pennsylvania (1933–45). Although most parts of the skin may be affected, most of the tumors are located in the extremities and generally beneath the nails of the fingers and toes (more than 50%, Bailey). They may occur on the genitalia of either sex (Grauer and Burt).

In about half of the tumors reported there was a previous history of trauma. The average duration of the lesions from the time of their appearance to the development of symptoms was 9 years. The tumors vary in size from 0.3 to more than 2 cm. in diameter. The smaller lesions are usually subungual, while the larger are present in easily distensible tissue. The variable size and pain depend at times on whether or not the tumors are under pressure. Most of the cases present a history of excruciatingly painful crises with radiation of the pain. All the subungual tumors are painful and slight brushing of the affected finger by the clothes or other slight pressure would be sufficient to produce a painful crisis. Scraping of the nail to great thinness was found to reduce the amount of pressure and diminish the pain (Raisman and Mayer). Tumors located in the soft tissues, such as the arms, legs and genitals, are painless. The pain is probably due to pressure and not entirely to a dis-

turbance of the sympathetic nerves since periarterial sympathectomy did not give relief (Burman and Gold).

Although the majority of the tumors occur singly, Weidman, Bergstrand, Stout and others reported cases of multiple tumors. The second case reported by Bergstrand offers the additional observation that there was a diminished density of the bones of the foot in which the multiple tumors occurred, which resembled multiple cysts. The tumors in his case occupied an intra-osseous position. This occurrence had not been reported previously, though others had observed rarefaction of the phalanges, as observed by Roentgen rays, at the site of the tumors. The pressure exerted by the expansile tumor is probably the cause of the demineralization of the contiguous bone. This appears to be a form of pressure atrophy (Grauer and Burt) rather than an atrophy of disuse, as was suggested by Stabins.

Grauer and Burt review the physiologic properties of glomus tumors. Systematic attempts to determine whether vasomotor reactions are associated with glomus tumors were made by Stabins and his associates.[268] They made local temperature studies before and after operation on 2 female patients who had subungual glomus tumors of the hand. Normally there is a synchronous drop in surface temperature in the hands on being immersed in cold water. However, after patients immersed their hands in water at 15° C., it was found that recovery to their previous temperature was more rapid on the involved side than on the uninvolved side; also that during immersion the temperature on the affected side did not drop as low as on the unaffected side. There was a difference of between 6° and 8° C. on the 2 sides. After operation, the temperature changes in the 2 hands were found to be synchronous. There was a vasodilatation in the skin of the affected member, which disappeared after the surgical removal of the tumor. However, the disappearance of the vasodilatation did not occur until about 8 weeks after surgical excision. Owing to the persistence of some pain at the site of operation, associated with vasodilatation, the authors considered the vasodilatation of the tumors as being caused by the painful sensory stimuli. This belief was strengthened by the fact that the vasodilatation disappeared when the pain ceased. Mason and Weil cited a case of Paulian and his associates in which there was an increased feeling of warmth and perspiration over the whole right side of the body in which the increase in temperature of from 0.5° to 2° C. was observed on the affected side. These changes disappeared following operation. Theis studied a person aged 69 who complained of intermittent claudication as a result of peripheral vascular disease associated with senile arteriosclerosis. Following treatment of alternating positive and negative pressure the circulation improved and the thermocouple temperature became normal. Six weeks after treatment for the claudication, a glomus tumor appeared on the leg. This was associated with sharp, agonizing pain and was followed by a peripheral drop in temperature, probably owing to an arterial spasm caused by the tumor. Excision of the tumor brought prompt relief and a return of the peripheral temperature to normal. The observations emphasize the physiologic effects produced by these tumors and indicate the association of the glomus with the maintenance of the temperature of the skin, whether through dilatation or constriction of the vessels. Theis suggested that under pathologic conditions congestion causes swelling with pressure on the nerves and consequent paroxysms of pain, while cold causes contraction of the muscular walls of the vessels with compression of the nerve fibers between the glomus cells and resulting pain. In either event, pressure is the important precipitating factor and whether or not the disturbance is a central one with involvement of the sympathetic system is still a moot question.

An excellent discussion of the pathology of the glomus is given by Weidman and Wise. The study of this article cannot be urged too strongly upon the reader.

"In brief, the neuromyo-arterial glomus is a normal vascular anastomosis which is distinctive in two respects: (1) it is arteriovenous, *i. e.*, there are not any intervening capillaries, the structure having a special and peculiar architecture; and (2) it includes special arrangement of muscle and nerve tissue. It occurs almost exclusively, as known at present, on the extremities, both upper and lower. It is supposed to play an important part in heat regulation. It assumes dermatologic significance when it becomes neoplastic, under which circumstances it is the vascular phase of this neuromyo-arterial complex which leads to the objective symptoms. It is probably the nerve phase of the complex which is responsible for the intolerable pain."

The glomus tumor, according to Weidman and Wise, is thus merely an exaggerated and disorderly glomus, attended by hyperplasia of its elements. It is exaggerated in that in most glomus tumors there is a new formation of Suquet-Hoyer canals. In a single histologic section there may be hundreds of larger and smaller ones, variously deformed and more or less intercommunicating, each being surrounded by its mantle of epithelioid cells and nerve fibers. It is disorderly in that the Suquet-Hoyer canal is not separately and purposefully aligned with the afferent artery on the one hand and with the primary collecting vein on the other. It is further disorderly in that the mantle of epithelioid cells is not at all uniform, *i. e.*, is thin in some places and excessively thick in others.

Weidman and Wise agree with Mason and Weil and others that this tumor should be regarded as a hamartoma rather than as a true neoplasm. The question of malignant change in glomus tumor is still *sub judice*. Ostrowski believes that a critical attitude should be maintained on this point and although no cases of malignancy following these tumors has been observed, it is still a possibility.

Love described a pin test for the diagnosis of glomus tumor:

"An ordinary steel pin is used. The patient is asked to indicate the maximal pain or tenderness. Oftentimes as the physician passes his finger toward the spot of the maximal pain, the patient will withdraw his extremity just as the patient with trigeminal neuralgia will withdraw his face when the trigger zones are approached. However, when the patient's confidence is gained and the point of a steel pin is used to examine around the lesion, the point of the pin can be pressed into the skin as near as 1 cm. to the lesion without producing severe pain, but just as soon as the point is pressed over the lesion, the patient will have an excruciating attack of the characteristic pain projecting from the lesion." One may be able to identify the lesion when it is not visible.

The glomus tumor can be removed only by complete surgical excision. Adair attempted to apply radiation in 1 case, using 1 square radium plaque of 700 mc. hours at 1 cm. distance and a 3 mm. brass filter. This treatment was repeated but caused no change in the tumor. Lewis and Geschickter applied 4 courses of Roentgen rays to a glomus tumor which had previously been diagnosed as Ewing's tumor, with no satisfactory results. One of the cases of Stabins and his co-workers failed to respond to 50 mg. hours of radium unfiltered. Stabins considered this as a therapeutic test verifying the diagnosis of glomus tumor. In 1 of Graves' and Burt's cases, which was at first considered hemangio-endothelioma, 4 courses of Roentgen treatment were given without any change in the size or character of the tumor. Two months after this treatment, the true nature of the tumor occurred to them. The stubborn resistance of the glomus tumor to all means of irradiation would tend to strengthen the objection to the so-called epithelioid cells being cells of embryonic character, particularly angioblasts, since all such cells are radiosensitive. Differential stains did not enlighten the authors as to the possible origin or nature of the glomus cells.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE DECLINE OF ACUTE SURGICAL MASTOIDITIS

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An analysis of the more recent communications appearing in the otologic literature indicates a decline in the incidence of acute surgical mastoiditis. Directly responsible for the decline is the widespread utilization of sulfonamides and penicillin—this despite such factors as seasonal variations, differing degrees of bacterial virulence, inadequate dosage, masking of symptoms, drug resistance, and toxic reactions. Indeed, the tenor of the current state of affairs may be summarized in the words of Bowers,[4a] who during the course of a presidential address before the American Otological Society declared: "With the advent of chemotherapy, the number of cases of mastoiditis and its sequelæ—particularly meningitis—has steadily declined. . . . The great decline in cases has already made it difficult to teach our resident physicians how to perform adequate mastoidectomies."

Despite the understandable conservatism of most otologists, pediatricians in general felt that sulfanilamide prevented extension of infection from the middle ear to the mastoid cells when treatment with sulfanilamide was employed during the winter of 1937–1938. In 1938 Horan and French[8] wrote of their experiences in an English naval hospital: the incidence of mastoiditis had fallen from 22.7 to 4.5% following the use of sulfanilamide in the treatment of acute purulent otitis media. The following year Fisher[7] presented a report on 180 cases: 92 patients were treated in the ordinary manner, and 88 were given sulfanilamide in addition to the usual form of treatment. In the group without sulfanilamide therapy there were 66 mastoidectomies. Mastoiditis developed in only 7 of the 88 patients who were given sulfanilamide.

In 1940, in a discussion of the rôle of chemotherapy in the treatment of complications of acute middle ear suppuration, Lindsay[10] stated: "The experience at the University of Chicago Clinics during the past 3 years has been that the number of operations necessary for acute mastoid suppuration has dropped materially, which apparently corresponds with general experience throughout the country." In 1942 De Sanctis[5] and his associates made a survey of 1992 cases of otitis media and mastoiditis in children hospitalized from 1931 to 1941. Comparison of the groups treated with and without sulfonamides from 1937 to 1941 showed a 9% incidence of mastoiditis in the former and 30% in the latter. Thus sulfonamides have played a dominant rôle in these changes of incidence. Bilchick and O'Kane[2] described a study in which 40 patients were treated with sulfanilamide, with 40 controls. The duration of discharge was reduced by one-third in the treated group, and the number who underwent mastoidectomy was reduced by one-half. Bowers[4b] employed chemotherapy over a 3 year period in 50% of his 793 cases of acute otitis media. The incidence of mastoidectomy was reduced about 50%.

Boies[3] reviewed his experiences with

650 cases of acute surgical mastoiditis during the years 1931 to 1941. From a study of the literature he concluded that a majority of the otologists and a larger majority of the pediatricians believe that sulfonamide therapy has been responsible for a distinct decrease in the incidence of acute otitis media and in the necessity for mastoid surgery in the mastoiditis complicating otitis media. Boies sent out a brief questionnaire to 30 otologists whose writings, or association with a public ward or teaching service, or geographic location made their viewpoints of special value. To the question "How much of a decreased incidence of acute surgical mastoiditis have you experienced in the past year or two (1940–1941)?" the answers were unanimous in the matter of decrease, with estimates of from 25 to 95%, particularly in private practice.

An investigation described by Falbe-Hansen and Becker-Christensen[6] in 1944 covered a total of 658 cases of acute suppurative otitis media, 323 in the control group and 335 in the treated group. The total number of patients included 419 under 15 years of age; 194 patients were treated with sulfapyridine, 31 with sulfathiazole. The average period of treatment was 7 days. The 3 organisms most frequently encountered in the pus from these ears were pneumococci, hemolytic streptococci, and Pfeiffer's bacilli. In the group treated with sulfapyridine, the period of discharge was reduced by 28%. Excluding patients who vomited, the reduction of discharge period was 40%. In the group treated with sulfathiazole, where vomiting was a rare occurrence, the reduction in discharge period was likewise 40%. In the control cases 9.3% required mastoid surgery, whereas in the groups treated with sulfonamides, 1.5% required operation.

A current review by House[9] of 3326 case histories of patients hospitalized at the Los Angeles County General Hospital because of otitis media before and after the general therapeutic use of sulfonamide drugs began elicited the following information: The number of patients hospitalized because of otitis media has decreased by 50%. In 4 of 5 patients with acute otitis media the pathologic process can be arrested within 3 days if the administration of sulfonamide compounds is instituted at the onset of symptoms. The incidence of mastoidectomy in patients hospitalized because of acute otitis media has been reduced by two-thirds. Spontaneous recovery occurs 1 week earlier in patients with acute otitis media who are treated with sulfonamide compounds. Surgical intervention was necessary approximately 1 week earlier when sulfonamide compounds were not administered. Postoperative drainage has been lessened by 1 week. The incidence of complications in cases of acute otitis media has been reduced by 20%. The mortality rate of otitic complications has been reduced by one-half. Before the advent of sulfonamide compounds as therapeutic agents, 9 of 10 persons with otitic meningitis died. With the therapeutic employment of sulfonamide compounds the rate is 1.5 to 10.

According to Weinstein and Atherton,[14] acute suppurative otitis media is a problem of great importance to physicians who encounter it either as an isolated disease or during the course of such infections as scarlet fever or measles. Improperly or inadequately treated, its complications may lead to partial or total loss of hearing and in some instances may seriously endanger life. Treating 50 cases of acute suppurative otitis media with penicillin, they found that complications were reduced to a minimum. Mastoidectomy was only an infrequent episode. In the experience of Swanson and Baker,[13] the use of penicillin frequently made it possible to avoid surgical intervention for acute mastoiditis. Smith[11] asserted that in cases of acute otitis media with clinical and roentgen evidence of mastoiditis, the clinical response to penicillin was prompt and often dramatic. It was believed that the drug was an important factor in cur-

ing the infection and sparing the patient mastoidectomy.

If penicillin is given early in acute otitis media, Struble[12] finds that the infection may be aborted. It must be given in adequate doses and over a sufficiently long period to prevent development of penicillin-resistant strains of bacteria and relapses. If given late, it may mask the infection and symptoms. If the surgical indications for drainage are still present, one resorts to myringotomy and mastoidectomy.

Twelve patients with acute suppurative otitis media complicating scarlet fever were treated with a sulfonamide compound by Ball[1]; penicillin was administered only after the infection had been demonstrated to be resistant to sulfonamide drugs. Of the 12 cases of acute otitis media complicating scarlet fever, 1 required surgical intervention. In 10 of the cases the otitis media responded rapidly to treatment; in 1 case recovery took place slowly. The 10 cases in which response to treatment was rapid showed resolution of the involvement of the tympanic membrane and restoration of normal hearing in from 1 to 2 weeks (average time 9 days). Ball considers the prompt resolution and healing of acute non-scarlatinal suppurative otitis media complicated by mastoiditis, without the necessity of surgical intervention, most promising. Five cases of acute non-scarlatinal otitis media complicated by mastoiditis were studied. Each patient had been under treatment with a sulfonamide compound and was given penicillin only after signs and symptoms of complicating acute mastoiditis had developed. Cessation of aural suppuration, abatement of all subjective signs and symptoms, and complete resolution of the process in the tympanic membrane were accomplished in from 3 to 18 days without resorting to surgical intervention.

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BOOK REVIEWS AND NOTICES

A TEXTBOOK OF BACTERIOLOGY AND IMMUNOLOGY. By JOSEPH M. DOUGHERTY, PH.D., Professor of Bacteriology, Villanova Coll., and ANTHONY J. LAMBERTI, Instructor in Bacteriology, Temple Univ., School of Medicine. Pp. 360; 102 illus. St. Louis: Mosby, 1946. Price, $4.50.

DESIGNED for pre-medical students or nurses studying medical bacteriology, this textbook offers the usual textbook material including a chapter on parasitic protozoa, on water, milk, and food examination, but nothing on pathogenic fungi. The content of the book is altogether too brief for undergraduate medical bacteriology. It stresses the early historical events in bacteriology and omits too many important modern developments and details. The greater part of the text could have been written more than 6 years ago without change of its present form. Exceptions are the chapters on chemotherapy, tuberculosis, and protozoa. The chapter on viruses considers only 4 virus diseases and bacteriophage. The rickettsioses considered are only epidemic typhus and Rocky Mountain spotted fever. To illustrate immunity, the old diagrams of Ehrlich are presented without consideration of recent advances. Inaccurate and misleading statements abound. Thus the statement is made that "typhus fever never develops in the absence of human body lice;" and subsequent treatment omits murine typhus completely. Judging this book in its entirety, it cannot be recommended for student use.

J. F.

ORAL MEDICINE. By LESTER W. BURKET, M.D., D.D.S., Professor of Oral Medicine, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania. Pp. 674; 350 ills. Philadelphia: Lippincott, 1946. Price, $12.00.

THIS is an excellent presentation of the various oral diseases and the various oral aspects of internal medicine. The book is well organized, comprehensive and thoroughly practical, as outlined in an introduction by J. L. T. Appleton. The first 200 pages deal with the various diseases of the oral mucosa, such as gingivitis, fusospirochetal infection, and the oral manifestations of metal poisoning, allergy and various skin diseases. The following 100 pages are devoted to the various diseases of the respiratory, cardiovascular, gastro-intestinal and urogenital systems. Then follow the disturbances of the endocrine glands and the diseases of the bones and joints. The remainder of the text is concerned with the vitamin deficiencies, the blood dyscrasias, the specific infectious granulomata, focal infection, oral pediatrics and gerodontics. The book is richly illustrated. As a special feature it is furnished with a color atlas showing a selected group of 60 commonly encountered oral lesions. Another feature is a regional diagnostic index of the more common sites of the various oral manifestations. Everywhere oral changes are presented as part of systemic disease. The book is highly recommended to dentists and physicians alike. It is felt that it is a "must" for all practitioners of the healing arts.

W. E.

HUMAN EMBRYOLOGY (PRENATAL DEVELOPMENT OF FORM AND FUNCTION). By W. J. HAMILTON, M.D., D.Sc., F.R.S.E., Professor of Anatomy, Medical College of St. Bartholomew's Hospital, University of London; J. D. BOYD, M.A., M.Sc., M.D., Professor of Anatomy, Medical College of the London Hospital, University of London; and H. W. MOSSMAN, M.S., Ph.D., Associate Professor of Anatomy, Univers, ity of Wisconsin. Pp. 374; 364 ills. Balti more, Williams & Wilkins, 1945. Price $7.00.

THIS is a welcome addition to the small group of current texts on human prenatal development. It is a wartime product of coöperation between British and American scholars and is a credit to all concerned. The authors show themselves to be thorough anatomists, interested in physiology, clear in their descriptions and modern in their

viewpoint. The morphology is unusually well illustrated by the English medical artist, A. K. Maxwell, who is very successful in his three dimensional pictures. These are important for the student, who has little opportunity of studying human embryology in the laboratory and for whom in consequence the descriptive text may be insufficient. For those interested in following up special topics the opportunity is provided by over 500 references to journals and books, given at the ends of chapters. Of the 16 chapters in the book the first 3 are concerned with germ cells and the cyclic changes in the female genital tract. Chapters 4 to 7 give the early stages of human development in the light of contemporary studies and include a photograph of the 7½ day human ovum of Rock and Hertig. The illustrations are from modern sources and replace the classic figures which have adorned text books of embryology for the last half century. Among these sources the publications of the Carnegie Laboratory of Embryology are prominent. Chapter 8 is concerned with theories and experiments since the time of Roux and bears the title, "Determination, Differentiation, The Organizer Mechanism, Abnormal Development and Twinning." These represent the modern attempt to learn something of the forces that underlie the complex changes which result in the functioning individual. Chapters 9 to 15 give the organogeny of the several systems, and here again one is impressed with the clearness of the illustrations and the effective use of color. The last chapter is entitled Comparative Vertebrate Development and shows useful figures of the fetal membranes and placenta in domestic animals such as pig, sheep, dog, rabbit and other rodents. This book is designed for the serious student, but all can profit from it and especially from the illustrations. W. A.

AN OUTLINE OF ORGANIC NITROGEN COMPOUNDS. By ED. F. DEGERING and Collaborators, Department of Chemistry, Purdue University. Pp. vi, 752. Ypsilanti, Mich.: Lithoprinters, 1945. Price, $7.50.

THIS book which presents in outline form the chemistry of the important nitrogen compounds is more than a revision of the volume which appeared under the same title in 1942. It is essentially a new book with respect to content and organization. There are 45 chapters dealing with such topics as General Concepts, The Fixation of Nitrogen, The Ammonia System of Compounds, The Nitroalkanes, Polynitroalkanes, Aromatic Nitro Compounds, Oximes, Aliphatic Amines, Amino Acids, Polypeptides and Proteins, the Diazenes, Aromatic Amines, Alkanolamines, Aromatic Diazo and Diazonium Compounds, Hydrazines, Urea and Its Derivatives, Guanidines, Organic Nitrogen Dyes, Alkaloids, Vitamins Containing Nitrogen, Synthesis of Nitrogen Ring Compounds, as well as many other related categories.

Each chapter is subdivided into sections on: (1) history, occurrence, structure, uses; (2) nomenclature; (3) methods of preparation; (4) physical properties; (5) reactions.

This outline will undoubtedly be more useful as a reference than as a textbook. It contains a wealth of material systematically arranged for the research chemist. S. G.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE. By CHARLES H. BEST, C.B.E., M.A., D.Sc. (London), F.R.S., F.R.C.P. (Canada), Professor and Head of Department of Physiology, Director of Banting-Best Department of Medical Research, University of Toronto; and NORMAN BURKE TAYLOR, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C. (Canada), M.R.C.S. (England), L.R.C.P. (London), Professor of Physiology, University of Toronto, Canada. Pp. 1169. Fourth ed. Baltimore: Williams & Wilkins, 1945. Price, $10.00.

THE world wide recognition that this lusty 9 year old has acquired hardly needs the confirmation of the "four editions and fourteen printings since 1937" and of Spanish and Portuguese editions. The linking of laboratory and clinic, very much in the limelight in these curriculum conscious days, is undoubtedly a large factor in the book's desired popularity. The emphasis on morbid physiology, rather than morbid anatomy is another indication—present in all editions to be sure—of the author's appreciation of modern trends and values. Up to date anatomists, physiologists, pathologists and internists should all feel at home in this wide-embracing volume. Though with its present additions it has now almost reached

maximum size, its small type (made tolerable by the use of double columns and generous heading) allows inclusion of an amount of material seldom found in a single volume.

The author's terse graphic style, the well chosen space-saving illustrations and the 57 pages of references, all add to the attractiveness of this excellent work. E. K.

SCIENTIFIC, MEDICAL, AND TECHNICAL BOOKS PUBLISHED IN THE UNITED STATES OF AMERICA, 1930–1944: A SELECTED LIST OF TITLES IN PRINT, WITH ANNOTATIONS. Edited by R. R. HAWKINS. Prepared under the direction of the National Research Council's Committee on Bibliography of American Scientific and Technical Books. Pp. 1114. Washington, 1946. ("Any inquiries concerning this bibliography may be addressed to United States International Book Association, 27 East 67th Street, New York City 21.")

CONCEIVED in the midst of war, this annotated list of approximately 6000 books (an equal number of available titles was rejected for one reason or another) has been brought to term in the amazing period of less than 2 years—approximately a year later than its sponsors had hoped, at that. In no other country in the world, probably, would a bibliographic project of such scope have been even attempted under like conditions—still less, achieved. Our American publishers, who succeeded in enlisting the aid of the Department of State, the National Research Council, and the Office of the Coördinator of Inter-American Affairs in the project, have reason indeed to congratulate themselves.

The list is intended primarily to provide other countries with descriptions of important scientific books published in the United States in the given period—*that are still in print*. The latter qualification, the omission of publications issued by states and territories, and the exclusion of some branches of the subjects treated, necessarily prevent the list from presenting a completely rounded and truly definitive picture of American scientific publications in these years. It is obvious, on the other hand, that a publication of this sort would not have been feasible at all, had not some restrictions been enforced. The list should admirably satisfy its primary purpose; but it is to be hoped that its clearly stated limitations will not be overlooked, now or subsequently, by researchers, librarians, and historians, to all of whom it can be very useful without serving as a definitive bibliography.

The annotations, which follow rather full analyses of the contents, "came," as the editor says, "from a variety of sources and inevitably reflect their origins." Many recall the language of the publishers' catalogues and announcements; some contain a fleeting critical comment (*e. g.*, "the style is dignified and sober"), but probably most are as objective as the purpose warrants. There are author and subject indexes, and an Appendix containing a directory of state agencies and a directory of publishers. The typography of the weighty volume has been excellently designed by Carl P. Rollins, Printer to Yale University. Of the editor and of the successive chairmen of the National Research Council's Committee (Harrison Craver, Hon. Sc.D., and John F. Fulton, M.D.), one can only say that the volume is an impressive tribute to their respective skills and stamina.

Having made such a handsome beginning, cannot all the forces concerned coöperate to keep the list up-to-date by issuing, say, quarterly or semi-annual supplements, which need not now suffer most of the restrictions enforced by the times on the present publication? If that were done, we should be offering to the world of science an even more valuable tool in the form of a reasonably definitive bibliography unique in our time and useful for all time. That would be wise and very practical diplomacy indeed.

W. McD.

THE ELECTRON MICROSCOPE. An Introduction to Its Fundamental Principles and Applications. By E. F. BURTON, Univ. of Toronto; and W. H. KOHL, Rogers Electronic Tubes, Ltd. 2nd ed. Pp. 325; 125 drawings, 136 light and electron micrographs. New York: Reinhold, 1946. Price, $4.00.

THIS book is written by the builders of the first electron microscope in America. It presents the elements of electron microscopy to the layman, advanced high-school students and members of those professions which have been influenced by this new science. The nature of light and of electron beams and the methods of focusing them are dealt with in a non-technical fashion,

the text being amply illustrated with cartoons and line drawings. The excellent selection of electromicrographs, biologic, bacteriologic, chemical, and metallurgic specimens is printed on high quality paper and represent a marked improvement over the 1st edition. While the significance of the micrographs is touched upon very lightly, an Appendix contains a complete bibliography of the entire field of electron microscopy up to 1944 for those who wish to delve further into particular developments in the field. T. A.

NURSING AND NURSING EDUCATION. By AGNES GELINAS, R.N. Pp. 72. Philadelphia: Commonwealth Fund, 1946. Price, $1.00.

THIS monograph marks an era in nursing which might be called its "coming of age." It is noteworthy that it originated in The Committee of the New York Academy of Medicine on "Medicine and the Changing Order." The inclusion of nursing both emphasizes its inseparable relationship to medicine and recognizes the emergence of nursing as a separate profession.

The contacts deal with the development of nursing; supply and demand in both world wars; personnel policies and recommendations including those for auxiliary workers; estimated supply and demand, and the future building of nursing.

This book is recommended for thoughtful study by nurses, physicians, and all concerned with the health of the community. It should be particularly helpful to members of Boards of hospitals and public health agencies.

The selection of the author as spokesman for nursing is a tribute to her proven ability in nursing education as well as her personal acceptability to both medical and nursing groups. T. L.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

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